Seggane Musisi · Stanley Jacobson
Editors

Brain Degeneration and Dementia in Sub-Saharan Africa

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ISBN 978-1-4939-2455-4 ISBN 978-1-4939-2456-1 (eBook)
DOI 10.1007/978-1-4939-2456-1

Library of Congress Control Number: 2015933379

Springer New York Heidelberg Dordrecht London

Printed on acid-free paper

Springer Science+Business Media LLC New York is part of Springer Science+Business Media (www.springer.com)

Foreword

It has long been repeated that the incidence of degenerative brain conditions such as Alzheimer disease is highest in countries with the longest life expectancy. It goes without saying, therefore, that as the conventional causes of early death and lifelong poor health in developing countries is mitigated, degenerative diseases will come to the fore and have the same devastating effect on people's lives and on the lives of their friends and families as they do in wealthier countries. What makes this book remarkable is that 20 years ago such a conversation would have been considered ridiculous or gratuitous. Now the problem of degenerative disease and brain injuries is all too real in Africa and other developing areas of the world. Take, for example, the recent WHO Global Burden of Disease Survey, which indicates that in low-income countries, Alzheimer's and other dementias have surpassed schizophrenia, alcohol dependence, bipolar disorder, asthma and, most stunningly, cerebrovascular disease in prevalence. At the same time, the health problems resulting from vitamin and nutritional deficiencies, HIV, malaria, and other environmental and communicable diseases remain in place.

The recognition of these epidemiologic shifts, coupled with the challenge of limited resources, has led to international health being among the most desired and highly subscribed opportunities in neurology, psychiatry and geriatric medicine residency programs. It appears that young people are voting with their feet by indicating a deep interest in brain diseases that are extant outside of their own countries.

When combined with the differing cultural norms of caring for the elderly among regions of the world, these facts take on a fascinating significance that will be of interest not only to physicians and epidemiologists, but to health planners, sociologists and anthropologists. By writing a book that crosses disciplines and takes a high level approach to nervous system diseases in Sub-Saharan Africa, Drs. Musisi and Jacobson have opened a new chapter in world neurology,

psychiatry and medicine in general. And, by giving details from an "on the ground" perspective in Mulago and places such as Kampala in Uganda, they have added verisimilitude to what could have been a theoretical exercise. Instead, this book springs to life with real problems, suffered by real people in an ever shrinking circle of human kind.

Harvard Medical School, Boston, MA, USA Allan H. Ropper
Brigham and Women's Hospital, Boston, MA, USA Raymond D. Adams

Preface

On the dates of February 1–3, 2012, a workshop conference was held at the scenic Golf Course Hotel in Kampala, Uganda, with the title: "Brain Degenerations and Emerging Mental Health Challenges in Sub-Saharan Africa". The impetus for this workshop originated from several meetings between Drs. Stanley Jacobson and Seggane Musisi when Dr. Jacobson was a Fulbright Scholar in the Department of Anatomy at the Makerere University College of Health Sciences in Kampala, Uganda, from 2011 to 2012. After several discussions on the causes of brain degeneration in Uganda, Drs. Jacobson and Musisi decided to invite several world authorities on causes of brain degeneration to present papers at a conference alongside Ugandan and other regional authorities on the subject. It was in this setting that world leaders on dementia were invited, including Drs. John Trojanowski and Virginia Lee from the University of Pennsylvania, who then came to Makerere University in Uganda to present their findings on dementias. The focus of the workshop was to discuss brain degenerations and emerging mental health challenges in Sub-Saharan Africa.

Makerere University in Kampala is Uganda's largest and second-oldest higher institution of learning in Africa, first established as a technical school in 1922. In 1963 it became the University of East Africa, offering courses leading to general degrees from the University of London. In 1970 it became an independent national university when the University of East Africa was split into three independent universities: University of Nairobi, University of Dar es Salaam and Makerere University.

Makerere University Medical School is the oldest medical school in *Eastern Africa*, having been part of the Makerere University, since 1924. The school provides medical education at diploma, undergraduate and postgraduate levels. Today, Makerere University offers programs for about 30,000 undergraduates and 3,000 postgraduates and it consists of the following nine colleges:

- College of Agriculture and Environmental Sciences
- College of Business and Management Sciences
- College of Computing Information Sciences

- College of Education and External Studies
- College of Engineering, Design, Art and Technology
- College of Health Sciences
- College of Veterinary Medicine, Animal Resources and Biosecurity
- College of Humanities and Social Sciences
- College of Natural Sciences

The teaching hospital for Makerere University is Mulago Hospital, a general hospital as well as a health center for the Kampala metropolitan area with an official bed capacity of 1790. Mulago Hospital was built in 1917, and Old Mulago Hospital merged with the New Mulago Hospital in 1960 to form the Mulago Hospital Complex as the National Referral Hospital. The complex also houses Makerere University College of Health Sciences.

About The Book

This book presents a summary of presentations made at the workshop on brain degeneration as seen in Uganda, Africa whose title and theme was "Brain Degenerations and Emerging Mental Health Challenges in Sub-Saharan Africa". It also presents the basic science, knowledge and understanding of brain degeneration including causes and management as well as the care burden for the affected as seen in Africa today. Case reports of real cases are presented and discussed.

The book is divided into six sections. The first section presents an overview of brain degenerations in sub-Saharan Africa. It also gives an introduction to the worldwide approaching epidemic of neuro-degeneration and in an ideal way of involving researchers and the community in its approach. Finally a look at a typical national referral hospital in a developing country, the Mulago national referral hospital in Kampala in Uganda, is given all complete with its daily limitations and overwhelming burden of disease in resource limited settings. The second section presents selected causes of brain degeneration in adults in Uganda as typifying Sub-Saharan Africa. The third section presents pediatric brain degenerations as seen in Uganda. Section IV discusses testing and investigating for brain degeneration in a setting of limited resources as seen in Uganda, sub-Saharan Africa. Case reports of actual cases of brain degeneration as seen in everyday practice in Africa are presented in Section V. Lastly Section VI deals with the care burden for dementia in the elderly in today's fast changing Africa with new socio-economic realities facing a society in transition.

Kampala, Uganda — Seggane Musisi
Boston, MA, USA — Stanley Jacobson

Acknowledgments

We wish to thank the Vice-Provost of Research of the University of Pennsylvania and the US Embassy in Kampala, Uganda, for their generous support. This workshop was also aided by the Fulbright Organization, Makerere University, Mulago Hospital, Tufts University, and USAID.

Workshop Poster

MAKERERE UNIVERSITY

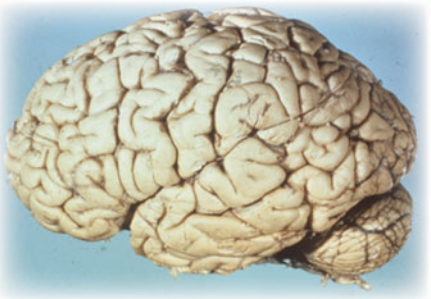
COLLEGE OF HEALTH SCIENCES

WORKSHOP - BRAIN DEGENERATIONS AND EMERGING MENTAL HEALTH CHALLENGES IN SUB-SAHARAN AFRICA

Guest Speaker: US Ambassador to Uganda, Jerry P. Lanier

VENUE: GOLF COURSE HOTEL, KAMPALA

Date: 1st - 3rd February, 2012



Banquet on 1st Feb 5-10pm

Secretariat & Presenters:

1. Stanley Jacobson
2. Nazarius M. Tumwesigye
3. David Basangwa
4. Noeline Nakasujja
5. Joseph Ochieng
6. James Tumwiine
7. Micheal Ssonko
8. Tom Olewe
9. Rosemary Byanyima
10. Paul Bangirana
11. Richard Idro
12. Joyce Kukafunda
13. Janet Nakigudde
14. Seggane Musisi
15. Jeffrey Griffiths
16. S. Matovu
17. Edward Ddumba
18. Zaven Khachaturian
19. Ethel Nakimuli
20. Gerry Schellenberg
21. John Trojanowski
22. Virgina Lee
23. Charles Ibingira

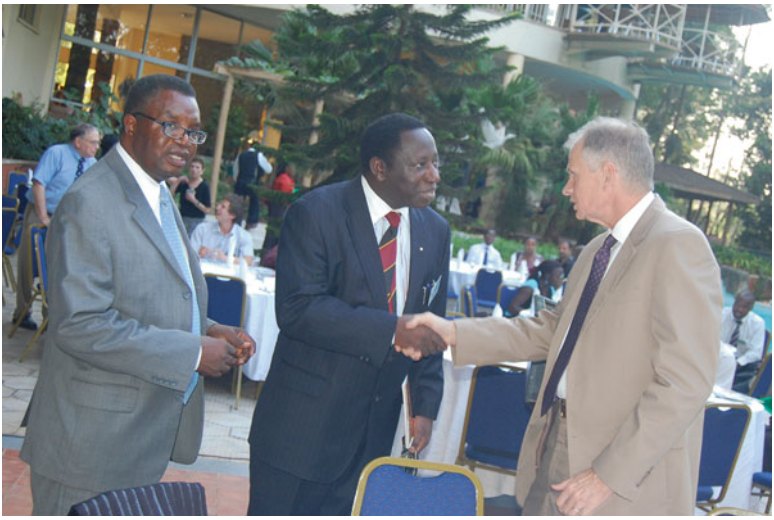
US Embassy Kampala | Fulbright Scholars | USAID | Mulago Hospital | Makerere University | University of Pennsylvania | Tufts University

Photos from Workshop

Avis Jacobson, Dr. Seggane Musisi and Connie Liu (Fulbright student in Uganda) welcome consul and US Ambassador to Uganda Jerry P. Lanier

Dr. S. Jacobson (Fulbright Scholar in Uganda) and Guest Speaker US Ambassador Jerry P. Lanier in discussion

Dr. John Trojanowski in discussion with Dean Charles Ibingira and Dr. Nazarius Tumwesigye



Dr. Seggane Musisi and Dean Charles Ibingira welcome US Ambassador Jerry P. Lanier

Professor Sewankambo, Principal of Makerere University, opening workshop

Dr. John Trojanowski giving post dinner Lecture

Dr. Jeffery Griffiths, Tufts University, discussing the public health issues associated with dementia

Contents

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Part I
Overview of Brain Degenerations in Sub-Saharan Africa

Chapter 1
The Penn ADCC: Integrating Neurodegenerative Disease Research Across Disciplines, Conditions, and Population Groups

John Q. Trojanowski, Steven E. Arnold, Jason H. Karlawish, Sharon X. Xie, and Vivianna Van Deerlin

Abstract Around the world, countries are experiencing seismic demographic changes due to rapid increases in the "oldest old", those over 85 years of age, and the young old "Baby Boomers" now aged 60–70 years (2014). While Americans are living longer and disability rates are declining, some 77 million began turning 60 in 2006, the time at which age-related early onset dementias begin. This, therefore, means that Alzheimer's Dementia (AD) and other dementias will increase with ominous consequences if we do not develop therapies to treat/prevent them. Thus, the number of Americans with AD will increase to over 13 million and delaying the onset of AD by just 5 years would reduce the number of AD patients and the cost of their care about 50 % by 2050. Intense efforts are urgently needed to develop disease modifying therapies for AD. AD is the most common but by no means the only type of dementia seen in older adults. In one U.S. study, AD accounted for 69.9 % of all cases of dementias, followed by vascular dementia (VaD) in 17.4 %. The remaining 12.7 % of cases were attributed to Parkinson's dementia (PD),

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S. Musisi, S. Jacobson (eds.), *Brain Degeneration and Dementia in Sub-Saharan Africa*, DOI 10.1007/978-1-4939-2456-1_1

normal-pressure hydrocephalus, frontal lobe dementia, alcoholic dementia, traumatic brain injury, and Lewy body dementia. Since there are shared mechanisms underlying many of these neurodegenerative diseases, there is much to be gained through joint research and clinical efforts and the sharing of data across disciplines, disease areas, and institutions.

Keywords Dementia • Amyotrophic lateral sclerosis (ALS) • Parkinson disease (PD) • Alzheimer's disease (AD) • Vascular dementia (VaD) • Institute on Aging

Introduction

Around the world, countries are experiencing seismic demographic changes due to rapid increases in the "oldest old", those over 85 years of age, and the young old "Baby Boomers" now aged 60–70 years (2014) [1–4]. While Americans are living longer and disability rates are declining [5], some 77 million began turning 60 in 2006, the time at which age-related early onset dementias begin. This, therefore, means that Alzheimer's Dementia (AD) and other dementias will increase with ominous consequences if we do not develop therapies to treat/prevent them. Thus, the number of Americans with AD will increase to over 13 million and Medicare costs for their care will increase to about $1 trillion by 2050 [6–10]. Since demography is the history of the future written now, the solvency of Medicare is in jeopardy. But, this future is malleable. Delaying the onset of AD by just 5 years would reduce the number of AD patients and the cost of their care about 50 % by 2050 [6]. Thus, intense efforts are urgently needed to develop disease modifying therapies for AD.

AD is the most common but by no means the only type of dementia seen in older adults. In one U.S. study [11], AD accounted for 69.9 % of all cases of dementias, followed by vascular dementia (VaD) in 17.4 %. The remaining 12.7 % of cases were attributed to Parkinson's dementia (PD), normal-pressure hydrocephalus, frontal lobe dementia, alcoholic dementia, traumatic brain injury, and Lewy body dementia. Since there are shared mechanisms underlying many of these neurodegenerative diseases, there is much to be gained through joint research and clinical efforts and the sharing of data across disciplines, disease areas, and institutions.

In anticipation of the "silver tsunami", the National Institutes on Aging (NIA) at the National Institutes of Health (NIH) launched initiatives to stimulate and support research and education on AD and related disorders in the mid-1980s [12, 13]. This resulted in landmark advances in the understanding, diagnosis and treatment of AD, related disorders, Mild Cognitive Impairment (MCI) and normal aging [14–19]. The Alzheimer's Disease Center (ADC) program was established by the NIA in 1984 as a means of promoting collaborations and building multi-site projects through a nationwide network of clinical and research programs. Today (2014) there are 28 ADCs throughout the country, including both AD Research Centers (ADRCs) and AD Core Centers (ADCCs). The ADCs have been instrumental in

promoting research and education on Alzheimer's disease (AD), related dementias, normal brain aging and mild cognitive impairment (MCI), as well as supporting development of better diagnostics and preventions/treatments for AD and related disorders and training researchers and care providers.

The University of Pennsylvania ADCC

The University of Pennsylvania established an ADCC in 1991, with the aim of advancing research by developing an infrastructure that could be leveraged across multiple disciplines and applied to the understanding of a broad range of neurodegenerative diseases. Today, the Penn ADCC has evolved into a highly interdisciplinary and seamlessly integrated Center with five Cores that collaborate extensively with other investigators at and beyond Penn, including other ADCs, the Alzheimer's Disease Cooperative Study (ADCS), the Alzheimer's Disease Education and Referral Center (ADEAR), the Alzheimer's Disease Neuroimaging Initiative (ADNI), The Alzheimer's Disease Genetics Consortium (ADGC), the National Cell Repository for Alzheimer's Disease (NCRAD), and the National Alzheimer's Coordinating Center (NACC). The Penn ADCC has been particularly active in two key areas: (1) expanding and integrating research on related dementias including fronto-temporal dementia (FTD), amyotrophic lateral sclerosis (ALS), and Parkinson disease (PD); and (2) developing novel techniques to address the challenges of conducting research on these disorders.

Penn has a long history of leadership in the field of aging. In 1979 the Center for the Study of Aging was established under the leadership of Vincent J. Cristofalo, a cell biologist internationally recognized for his work on understanding the mechanisms of cellular aging. In 1989, the Center was renamed the Institute on Aging (IOA), signifying a structure that cuts across schools, departments, and disciplines. While the IOA is centered in the University of Pennsylvania Perelman School of Medicine (UPPSOM), the approximately 200 IOA fellows and associate fellows represent researchers from Penn's Schools of Nursing, Veterinary Medicine, Dentistry, and Arts and Sciences, the Wharton School, The Children's Hospital of Philadelphia, The Wistar Institute, The Monell Chemical Senses Center, The Richard Stockton College of New Jersey, Widener University, Temple University, the Polisher Research Institute, and the Philadelphia Corporation for Aging.

Today, the IOA and the ADCC are two parts of larger network of resources at Penn focused on aging and age-related diseases (Fig. 1.1). These include the Center for Neurodegenerative Disease Research (CNDR), the Division of Geriatric Medicine, the Morris K. Udall Parkinson's Disease Center of Excellence, and the Marian S. Ware Alzheimer Program, a unique multidisciplinary program that supports drug discovery and clinical trial design, as well as studies focused on biomarkers of stress in AD and continuity of AD care. Penn is also home to the Biomarker Core of the ADNI and the ADGC; and has had/currently has three related Program Projects funded by the NIA: In Vitro and In Vivo Models of AD;

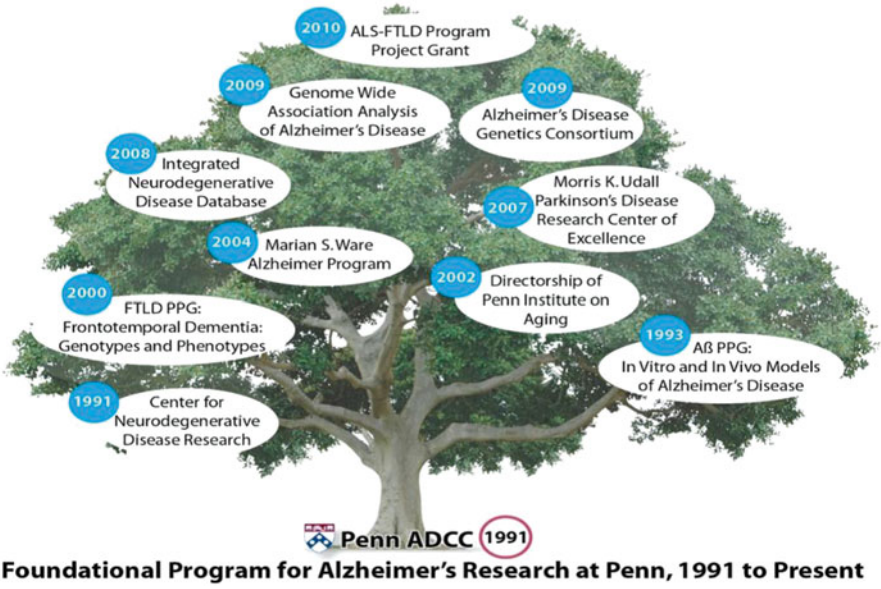

Fig. 1.1 The Penn ADCC is the foundation (*roots and trunk*) for all programs on aging, AD, and related disorders at Penn (*branches*) as depicted for representative programs

Frontotemporal Dementia: Genotypes and Phenotypes; and most recently TDP-43 Proteinopathies in ALS Dementia. These program projects reflect Penn's focus on dementias other than AD as well as comorbid conditions that impact on the manifestation of disease; and the fact that over the past several decades, Penn has been at the vanguard of molecular biological research on neurodegenerative disease.

The goals of the Penn ADCC are implemented through five cores as well as a pilot grant program and collaborations within and beyond the Penn campus. Working together, the five Cores advance an aggressive, integrated research program that has resulted in major discoveries about the mechanisms underlying neurodegenerative diseases and contributed to the development of new diagnostic and treatment approaches. The integration of research among the Cores begins with the Clinical Core, which assesses and follows patients with cognitive impairments due to AD or other dementias through its recently expanded Penn Memory Center. While clinical evaluations are important, the primary mission of the Core is to advance clinical research, both by conducting clinical trials and acquiring biofluids, tissues, DNA, and imaging studies that can be used in a research studies conducted by investigators in the Neuropathology, Biomarkers, and Genetics Core as well as international collaborative studies such as NACC, ADNI and ADGC. Through participation in ADNI, Penn ADCC investigators have developed promising new technologies, including florbetapir (18 F-AV-45), an amyloid imaging agent for use with positron emission tomography (PET) to detect plaques in the brain of living persons [20]; and a cerebrospinal fluid (CSF) biomarker signature defined by Abeta1-42 and

total tau (t-tau) that identifies individuals with mild AD and predicts conversion from MCI to AD [21]. Enrollment of subjects in these studies is dependent on the efforts of the Education, Recruitment and Retention Core; and analysis of data collected in these studies is conducted by the Data Management and Biostatistics Core. Meanwhile, the Administrative Core provides administrative oversight for the entire program and administers the pilot grant program.

Integration Across the Spectrum of Neurodegenerative Diseases

Through collaborations with other Penn-based programs on aging and age-related diseases, the Penn ADCC has integrated research and clinical care across the spectrum of neurodegenerative diseases. Collaborations with the CNDR, in particular, have contributed to a dramatic expansion in basic and clinical research on AD and related disorders as well as investigations into the etiology, pathogenesis, diagnosis, treatment and prevention of these neurodegenerative diseases. The CNDR functions as a "center without walls," wherein investigators collaborate in multidisciplinary clinical and basic research to increase understanding of the causes and mechanisms leading to brain dysfunction and degeneration in AD, PD, FTD, ALS and related disorders that occur increasingly with advancing age. CNDR promotes a number of important research initiatives such as the development of new and effective therapies and finding a cure for devastating aging related neurodegenerative diseases through a number of mechanisms.

For example, there has been considerable excitement at Penn with regard to the discovery of TDP-43 (the ubiquitinated TAR DNA-binding protein 43) as the disease protein that provides a molecular link between ALS and a subtype of FTD called FTLD-U (Frontotemporal lobar dementia with ubiquitinated inclusions). Using postmortem brain tissue collected through the ADCC's Neuropathology, Genetics, and Biomarker Core, CNDR investigators showed in late 2006 that mutated TDP-43 accumulated as a misfolded protein in the hippocampus, neocortex, and spinal cord of individuals diagnosed with FTLD-TDP and ALS [22]. Subsequently, multiple pathogenic mutations in TDP-43 were found to be associated with ALS [23] and a number of other studies identified additional TDP-43 mutations associated with ALS and FTLD. An international collaboration led by researchers at the Penn ADCC and involving 13 countries resulted in the identification of a protein called TMEM106B, which represents a risk factor for FTLD-TDP [24].

The Penn ADCC also works closely with the NINDS Morris K. Udall Parkinson's Disease Center of Excellence at Penn to study the molecular mechanisms underlying movement and cognitive impairments in PD, as well as the care and treatment of patients and training of physicians. Penn is one of only six institutions that have both a Udall Center and an ADC. The theme of the Penn Udall Center is cognitive impairment, a very understudied aspect of PD. Areas of shared research interest between these two Centers is exemplified by recent biomarker collaborations which

showed that the same low CSF Aβ42 levels that are signatures of AD also predict cognitive decline in PD [25], while plasma EGF levels correlate with cognitive performance and predict cognitive impairment in PD, but not in AD [26].

All of these biomarker and genetics studies accumulate massive amounts of data, and rely on resources provided by the Data Management and Biostatistics Core for data analysis. The Core recently launched an Integrated Neuro-Degenerative Disease (INDD) database inspired by NACC. This relational database includes data on AD, PD, ALS, FTLD and related diseases studied by ADCC and affiliated Penn investigator groups. A recent study compared the INDD database against a more traditional database approach where each center operates its own separate database, and concluded that the integrated database excelled in easing the process of querying and extracting data, thus producing results more quickly and with fewer errors [27].

Integrating Across Population Groups

Another unique feature of the Penn ADCC is its focus on dementia among Latino and African Americans. Latinos are at least one and one-half times more likely than whites to develop dementia [28], and African-Americans two times as likely [29], yet these population groups are less likely to participate in research. Consequently, the reasons for their increased risk are unclear. The Penn ADCC received a supplemental ADC grant in 1993 to develop a Latino cohort. In a collaborative study with four other ADCs, they found that after adjusting for education, Latinos in the United States develop AD almost 7 years earlier than Whites [30]. Subsequent research by the Penn ADCC showed that elderly Latinos in Philadelphia, who are primarily immigrants from Puerto Rico, not only have an earlier age of onset but more severe cognitive impairment [31].

Genetic studies on patients in the Latino cohort led to the identification of three families in whom a PSEN1 G201A mutation was found. This mutation was reported previously in Caribbean-Hispanics [32], prompting Penn geneticists to test all available Latino samples in the Penn ADCC DNA bank (n = 282) for the mutation. Remarkably, the mutation was found in ~12 % (12/103) of AD cases in the Latino cohort who were *unselected* for family history. This suggests that the mutation may be more prevalent than previously recognized in this population.

Another study identified the first reported case in an African American of a mutation in the microtubule-associated protein tau (MAPT) gene, which is associated with a rapidly progressive form of familial FTD [33]. Imaging, CSF biomarker, and clinical studies of this patient, as well as post-mortem examination of her brain provided additional clues about the neuropathology underlying this disease. Yet none of these studies would be possible without the participation of individuals in minority communities. This is where the Education, Recruitment, and Retention Core comes into play. For example, the Penn ADCC is also increasingly reaching out to the African American community in West Philadelphia, where the University is located.

New Directions

To achieve the goal of preventing or ameliorating AD and related diseases as well as to promote successful aging, the Penn ADCC has also developed novel partnerships with philanthropic organizations to take its research, education and outreach programs in new directions. One such initiative is the Marian S. Ware Alzheimer Program, which was launched with generous multi-million dollar philanthropic support from the Ware family in January 2004 to comprehensively attack the problem of AD [34]. The Ware Program includes four key components: (1) AD Drug Discovery; (2) AD Clinical Trial Design; (3) Biomarkers of Stress in Normal Aging and AD; and (4) Continuity of AD Care, a project of the University of Pennsylvania School of Nursing. This Program enables the ADCC to expand its role in drug discovery neurodegenerative diseases by bridging the gap between drug target identification, validation and proof of concept studies, and to hasten efforts to bring new therapies out of laboratories into the clinic.

Partnerships are also being forged between the Penn ADCC and pharmaceutical companies. For example, an ADCC-linked AD drug discovery partnership with Johnson and Johnson, Inc. and a cooperative agreement between the Penn Chemistry Department and the NIA is pursuing chemical synthesis of different classes of microtubule stabilization drugs to identify the best class of compounds that enter the brain to stabilize microtubules for the treatment of AD and related tauopathies [35].

The Penn ADCC and IOA also support 1-year pilot grants designed to encourage researchers from disparate fields to turn their attention and expertise toward investigations of dementia. In 2011–2012, 10 pilot grants with were supported. Two of these, funded by the ADCC, will focus on Alzheimer's disease (AD) and related neurodegenerative disorders. The remaining pilots, supported by funding from Penn's School of Medicine and The Bingham Trust, focused on aging and aging related diseases.

The Penn ADCC has also been working with other Penn faculty and the Campaign to Prevent Alzheimer's Disease by 2020 (PAD2020) to convert the Penn ADCC into a prototype model of a Comprehensive Alzheimer's Disease Center (CADC) modeled on the National Cancer Institute's Comprehensive Cancer Centers [36]. CADCs would serve as coordinating hubs of existing ADCs, facilitating expanded multidisciplinary and multisite collaborative research studies and integrating active programs in clinical care and clinical trials. The CADC concept was introduced at a symposium in 2008 [37] and incorporated into the Alzheimer's Study Group report that was presented to the U.S. Senate Committee on Aging in 2009 [38]. The Penn CADC would comprise a number of interacting teams, each of which would include both research and clinical components. With an executive/administrative committee as its hub, the teams would address issues related to: training; clinical care; healthy brain aging; genetics; biomarkers; neuropathology; neuroimaging; data management, computational modeling, and biostatistics; drug discovery; integration of care; health policy, comparative, and cost effectiveness; and outreach, education, and dissemination.

Spreading the Message

A final important mission of the Penn ADCC is to increase scientific and public awareness of AD and healthy brain aging in order to advance the research mandate. This is exemplified by the production of two public education films – *Shining a Light on AD* and *Taking Steps to Healthy Brain Aging* – funded by the MetLife Foundation in collaboration with three other ADCs and Penn's IOA and CNDR. MetLife then supported "re-purposing" these two films into a single film for PBS called *Alzheimer Disease – Facing the Facts,* which aired on more than 90 % of PBS outlets in 2009–2010, won the 2008 CINE Golden Eagle Award, and won a 2009 Emmy Award for documentary program (for more details, see http://www.alzheimersfacingthefacts.org/). In addition to spearheading production of these films, the Education, Recruitment and Retention Core provides other educational materials for patients and caregivers and provides.

Conclusion

In summary, the Penn ADCC forms partnerships at and beyond Penn to meet the global challenges of rapidly aging populations and the epidemic of AD and related disorders. These partnerships have enabled the Penn ADCC to accomplish its mission through research on AD and related disorders as well as normal aging, and through education to increase understanding of these disorders and accelerate the pace of developing better diagnostics and therapies for AD and related dementias.

References

1. Federal Interagency Forum on Aging-Related Statistics. Older Americans 2004: key indicators of well-being. Washington, DC: U.S. Government Printing Office; 2004.
2. Hetzel L, Smith A. The 65 years and over population: 2000, Census Bureau brief, C2KBR/01-10. Washington, DC: U.S. Census Bureau; 2001.
3. Meyer J. Age: 2000, Census Bureau brief, C2KBR/01-12. Washington, DC: U.S. Census Bureau; 2001.
4. Rowe JW, Kahn RL. Successful aging. New York: Pantheon Books; 1998.
5. Manton KG, Gu X, Lamb VL. Change in chronic disability from 1982 to 2004/2005 as measured by long-term changes in function and health in the U.S. elderly population. Proc Natl Acad Sci U S A. 2006;103:18374–9.
6. Brookmeyer R, Gray S, Kawas C. Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. Am J Public Health. 1998;88:1337–42.
7. Cogan JF, Mitchell OS. Perspectives from the President's commission on social security reform. J Econ Perspect. 2003;7:149–72.
8. Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA. Alzheimer disease in the US population: prevalence estimates using the 2000 census. Arch Neurol. 2003;60:1119–22.

9. Jedrziewski MK, Lee VM, Trojanowski JQ. Lowering the risk of Alzheimer's disease: evidence-based practices emerge from new research. Alzheimers Dement. 2005;1:152–60.
10. The Lewin Group. Saving lives, saving money: dividents for Americans investing in Alzheimer research. Alzheimer's Association report. 2006.
11. Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR, Ofstedal MB, Burke JR, Hurd MD, Potter GG, Rodgers WL, et al. Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology. 2007;29:125–32.
12. Hodes RJ. Public funding for Alzheimer disease research in the United States. Nat Med. 2006;12:770–3.
13. Hodes RJ, Buckholtz N, Cahan V, Morrison-Bogorad M. Eyes on the prize: federal Alzheimer's research effort aims to facilitate interventions. Alzheimers Dement. 2008;4:S37–47.
14. Goedert M, Spillantini MG. A century of Alzheimer's disease. Science. 2006;314:777–81.
15. Ho GJ, Drego R, Hakimian E, Masliah E. Mechanisms of cell signaling and inflammation in Alzheimer's disease. Curr Drug Targets Inflamm Allergy. 2005;4:247–56.
16. Markesbery WR. Neuropathologic alterations in mild cognitive impairment: a review. J Alzheimers Dis. 2010;19:221–8.
17. Palop JJ, Mucke L. Amyloid-beta-induced neuronal dysfunction in Alzheimer's disease: from synapses toward neural networks. Nat Neurosci. 2010;13:812–8.
18. Perrin RJ, Fagan AM, Holtzman DM. Multimodal techniques for diagnosis and prognosis of Alzheimer's disease. Nature. 2009;461:916–22.
19. Walsh DM, Selkoe DJ. Deciphering the molecular basis of memory failure in Alzheimer's disease. Neuron. 2004;44:181–93.
20. Choi SR, Golding G, Zhuang Z, Zhang W, Lim N, Hefti F, Benedum TE, Kilbourn MR, Skovronsky D, Kung HF. Preclinical properties of 18F-AV-45: a PET agent for Abeta plaques in the brain. J Nucl Med. 2009;50:1887–94.
21. Shaw LM, Vanderstichele H, Knapik-Czajka M, Clark CM, Aisen PS, Petersen RC, Blennow K, Soares H, Simon A, Lewczuk P, et al. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. Ann Neurol. 2009;65:403–13.
22. Neumann M, Sampathu DM, Kwong LK, Truax AC, Micsenyi MC, Chou TT, Bruce J, Schuck T, Grossman M, Clark CM, et al. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Science. 2006;314:130–3.
23. Van Deerlin VM, Leverenz JB, Bekris LM, Bird TD, Yuan W, Elman LB, Clay D, Wood EM, Chen-Plotkin AS, Martinez-Lage M, et al. TARDBP mutations in amyotrophic lateral sclerosis with TDP-43 neuropathology: a genetic and histopathological analysis. Lancet Neurol. 2008;7:409–16.
24. Van Deerlin VM, Sleiman PM, Martinez-Lage M, Chen-Plotkin A, Wang LS, Graff-Radford NR, Dickson DW, Rademakers R, Boeve BF, Grossman M, et al. Common variants at 7p21 are associated with frontotemporal lobar degeneration with TDP-43 inclusions. Nat Genet. 2010;42:234–9.
25. Siderowf A, Xie SX, Hurtig H, Weintraub D, Duda J, Chen-Plotkin A, Shaw LM, Van Deerlin V, Trojanowski JQ, Clark C. CSF amyloid {beta} 1–42 predicts cognitive decline in Parkinson disease. Neurology. 2010;75:1055–61.
26. Chen-Plotkin AS, Hu WT, Siderowf A, Weintraub D, Goldmann Gross R, Hurtig HI, Xie SX, Arnold SE, Grossman M, Clark CM, et al. Plasma epidermal growth factor levels predict cognitive decline in Parkinson disease. Ann Neurol. 2011;69:655–63.
27. Xie SX, Baek Y, Grossman M, Arnold SE, Karlawish J, Siderowf A, Hurtig H, Elman L, McCluskey L, Van Deerlin V, et al. Building an integrated neurodegenerative disease database at an academic health center. Alzheimers Dement. 2011;7:e84–93.
28. Gurland BJ, Wilder DE, Lantigua R, Stern Y, Chen J, Killeffer EH, Mayeux R. Rates of dementia in three ethnoracial groups. Int J Geriatr Psychiatry. 1999;14:481–93.
29. Potter GG, Plassman BL, Burke JR, Kabeto MU, Langa KM, Llewellyn DJ, Rogers MA, Steffens DC. Cognitive performance and informant reports in the diagnosis of cognitive impairment and dementia in African Americans and whites. Alzheimers Dement. 2009;5:445–53.

30. Clark CM, DeCarli C, Mungas D, Chui HI, Higdon R, Nunez J, Fernandez H, Negron M, Manly J, Ferris S, et al. Earlier onset of Alzheimer disease symptoms in latino individuals compared with anglo individuals. Arch Neurol. 2005;62:774–8.
31. Livney MG, Clark CM, Karlawish JH, Cartmell S, Negron M, Nunez-Lopez J, Vega IE, Entenza-Cabrera F, Arnold SE. Ethnoracial differences in the clinical presentation of Alzheimer's disease at an urban Alzheimer's disease center. Am J Geriatr Psychiatry. 2011;19:430–9.
32. Athan ES, Williamson J, Ciappa A, Santana V, Romas SN, Lee JH, Rondon H, Lantigua RA, Medrano M, Torres M, et al. A founder mutation in presenilin 1 causing early-onset alzheimer disease in unrelated Caribbean Hispanic families. JAMA. 2001;286:2257–63.
33. Van Deerlin VM, Forman MS, Farmer JM, Grossman M, Joyce S, Crowe A, Trojanowski JQ, Lee VM, Chatterjee A. Biochemical and pathological characterization of frontotemporal dementia due to a Leu266Val mutation in microtubule-associated protein tau in an African American individual. Acta Neuropathol. 2007;113:471–9.
34. Trojanowski JQ, Arnold SE, Karlawish JH, Naylor M, Brunden K, Lee M-Y. Improving the treatment and care of Alzheimer patients through interdisciplinary research. Alzheimers Dement. 2012;8:564–73.
35. Brunden KR, Zhang B, Carroll J, Yao Y, Potuzak JS, Hogan AM, Iba M, James MJ, Xie SX, Ballatore C, et al. Epothilone D improves microtubule density, axonal integrity, and cognition in a transgenic mouse model of tauopathy. J Neurosci. 2010;30:13861–6.
36. Trojanowski JQ, Arnold SE, Karlawish JH, Brunden K, Cary M, Davatzikos C, Detre J, Gaulton G, Grossman M, Hurtig H, et al. Design of comprehensive Alzheimer's disease centers to address unmet national needs. Alzheimers Dement. 2010;6:150–5.
37. Khachaturian ZS, Snyder PJ, Doody R, Aisen P, Comer M, Dwyer J, Frank RA, Holzapfel A, Khachaturian AS, Korczyn AD, et al. A roadmap for the prevention of dementia II: Leon Thal symposium 2008. Alzheimers Dement. 2009;5:85–92.
38. Alzheimer's Study Group. A national Alzheimer's strategic plan. The report of the Alzheimer's study group. Accessed online at www.alz.org/documents/national/report_ASG_alzplan.pdf (2009).

Chapter 2
Anatomy of Normal and Degenerative Changes in the Brain

Samuel S. Giles, Rosemary Kusaba Byanyima, and Stanley Jacobson

Abstract This chapter reviews the normal anatomy of the human cerebrum. We then demonstrate the appearance of degenerative changes in the brain grossly and with CT and MRI images. We have focused on the effects on the cerebrum of major diseases that affect the cerebrum, namely: (1) CVA/strokes; (2) the Communicative diseases of malaria and HIV/AIDS and, (3) Non-Communicable Disease (NCD) the Neurodegenerative diseases-Alzheimer's' Disease, Amyotrophic Lateral Sclerosis, Frontotemporal degeneration/Picks, Huntington's' Disease, Parkinson's'. For each of the diseases we have included an illustrative case history. We have also listed the division of the NIH, WHO or the CDC and the organization which provides assistance to the patients and the families that are affected by these diseases.

Keywords Cerebrovascular accidents • Communicative diseases • Non-Communicable Diseases • Neurodegenerative diseases • Case history

Abbreviations

AD	Alzheimer's Disease
ALS	Amyotrophic Lateral Sclerosis
CDC	Center for Disease Control
CVA	Cerebrovascular Accident
DICOM	Digital Imaging and Communications in Medicine format
HD	Huntington's' Disease

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S. Musisi, S. Jacobson (eds.), *Brain Degeneration and Dementia in Sub-Saharan Africa*, DOI 10.1007/978-1-4939-2456-1_2

HIV/AIDS	Human immunodeficiency virus infection and acquired immunodeficiency syndrome
NCD	Non-communicable diseases
PD	Parkinson's' Disease
WHO	World Health Organization

Introduction

It is appropriate that this workshop was in Uganda discussing normal and abnormal findings in the brain in the region of Africa where genetic and fossil evidence supports a recent (<200,000 year) origin of modern *Homo sapiens* in Africa [1]. This was then followed by later population migrations and dispersal across the world as the "Out of Africa" model [2]. The fossil record further suggests that for over one half of mankind's life, *Homo sapiens* and their ancestors "Lucy" lived in sub-Saharan Africa [3, 4].

Data from the World Health Organization [5] and the Center for Disease Control [6] demonstrates the similarity in brain diseases seen throughout the world with major differences noted due to income disparities which directly affect public health and longevity. In sub-Saharan Africa currently HIV/AIDS, sleeping sickness, malaria, and sickle cell anemia are the common diseases in the region [7] with road traffic accidents becoming another common cause of injury to the brain in the African region [8, 9].

Data from the WHO shows that as the public health improves in low-income countries due to economic strengthening, there is a concomitant lengthening of one's life and a shift from the communicative diseases (lower respiratory infections, diarrheal diseases, HIV/AIDS, malaria, and TB; [5]) being the primary causes of death to the non-communicable diseases (NCD-Cardiovascular, Cancer, Respiratory, Diabetes, and Neurodegenerative diseases) being as the primary cause of death. The non-communicable diseases which are the most common cause of death in the mid- to high income countries include; cardiovascular disease, stroke and other cerebrovascular diseases, cancers and a concomitant rise of dementias including Alzheimer's disease [5].

Since the cerebral hemispheres are the region in the brain most commonly affected by degenerative diseases [10], we will focus our discussion on the diseases that most commonly affect the cerebrum. A detailed classification of disease affecting the cerebrum can be seen in *Principles of Neurology* [11]. We have reviewed the records of over 500 patients CT imaged at the Mulago Teaching Hospital in Kampala over the last several years and we noted the similarity in the common causes of disease in the brains there and in the United States – stroke and other cerebrovascular diseases, HIV/AIDS, Neurodegenerative diseases, (Parkinson disease, Alzheimer's) alcoholism, and motor vehicle accidents also becoming a major cause. In the US the accidents are primarily in automobiles while in Uganda and the lower income countries the accidents are primarily with the smaller motor cycles called "boda-bodas" in Uganda which are widely used throughout East Africa and in other lower income countries [12].

Our discussion will first review the normal anatomy of the cerebral hemispheres and we will then focus on the three major categories of diseases that affect the cerebrum. In Group One we have included the principle disease that causes degeneration in the brain, cerebrovascular/stroke, in Group Two we have illustrated the effects of the most common communicative diseases – malaria and HIV on the cerebrum, and in Group Three we include the major NCD, Neurodegenerative Diseases-AD, PD, HD, and ALS. There are other causes of cerebral degeneration including alcoholism, malnutrition, environmental toxins and trauma which are discussed elsewhere in this book.

Materials and Methods

With post-mortem examination of the brain limited in Uganda, in this chapter, we illustrate the gross features of degenerative diseases of the cerebrum with specimens from several sources- the anatomy laboratory at Tufts University School of Medicine, the Department of Pathology at Tufts Medical Center, and the Department of Neurology at University of Massachusetts in Worcester. The cases of malaria that we refer to in this book are all from Mulago Hospital in Kampala Uganda and were reviewed in the Department of Radiology at Mulago Hospital. We have included on our www.braindementia.net an illustrative video from one of the patients with malaria seen at the Kampala Imaging center in Kampala which illustrated many of the findings seen with cerebral malaria which are also discussed in other chapters in this book.

Virtual Patients

With the Health Insurance Portability and Accountability Act of 1996 (HIPAA US Department of Health and Human Resources [13]) limiting the amount of information that one can reveal from each patient, we have respected this policy and consequently created for this paper Eight Virtual Patients that illustrate the findings in each disease. A Virtual Patient is a patient created electronically or on paper from real patient data [14]. These Virtual patients are widely used for educating health care workers [15, 16]. Our virtual patients were created by a team effort combining the identified cause of death, with gross or CT observations, and the clinical expertise of our colleagues to create a plausible patient. For each case we will present first a short case history including medical and neurological information, and then we will illustrate the pathological findings with gross specimens and CT or MRI images from the actual patient under discussion or from a patient with similar findings.

Illustrative Video

We developed a video demonstrating a virtual patient with Cerebral Malaria and stored it on our website (Cerebral malaria, www.braindementia.net) from a case of cerebral Malaria which demonstrates cortical atrophy, a subdural, and dilation of the ventricles, We created a video using the OsiriX open software program (OsiriX: 2004) on a Macintosh PRO Processor: 2 × 3 GHz Quad-Core Intel Xeon Memory to organize the DICOM images (Digital Imaging and Communications in Medicine, the standard format used in CT and MRI imaging worldwide). The images were collected from a MX 16 Philips CT Scanner Philips. The video was created from the stack of DICOM images using QuickTime Pro. We also inserted labeled JPEG images to illustrate major findings in each movie using Adobe Photoshop and strung into the exported movie using QuickTime Pro.

Observations

Normal Anatomy of the Gross Brain (Fig. 2.1a–c from Jacobson and Marcus [17]). In Fig. 2.1a we have labelled the lateral surface of the brain with the frontal, parietal, occipital, and temporal gyri and sulci identified. In Fig. 2.1b on the medial surface of the brain we have identified the gyri and sulci in the frontal, parietal, occipital, temporal and cingulate gyrus of the brain. In Fig. 2.1c we review the insular region deep in the lateral sulcus.

Group One- CVA/Strokes

Worldwide, cardiac disease and stroke are the most common causes of death in the middle and upper income countries while in the lower income countries respiratory infections is the most common cause, followed by diarrheal disease, HIV AIDS and then ischemic heart disease, as the fourth most common, followed by malaria and then stroke [5].

In the USA as noted in the most recent data from the CDC in 2011, cardiac disease is the most common cause of death (597,689) with cancer as second (574,743), chronic lower respiratory diseases third (138,080) and CVA/stroke the fourth most common cause of death (129,476). Alzheimer's Disease is the 6th most common cause of death (83,494). Strokes also are the most common cause of degeneration in the brain and untreated hypertension in many cases is the root cause and can lead to strokes, ministrokes/TIAs, mild cognitive dysfunction and dementia. The following cases illustrate these points.

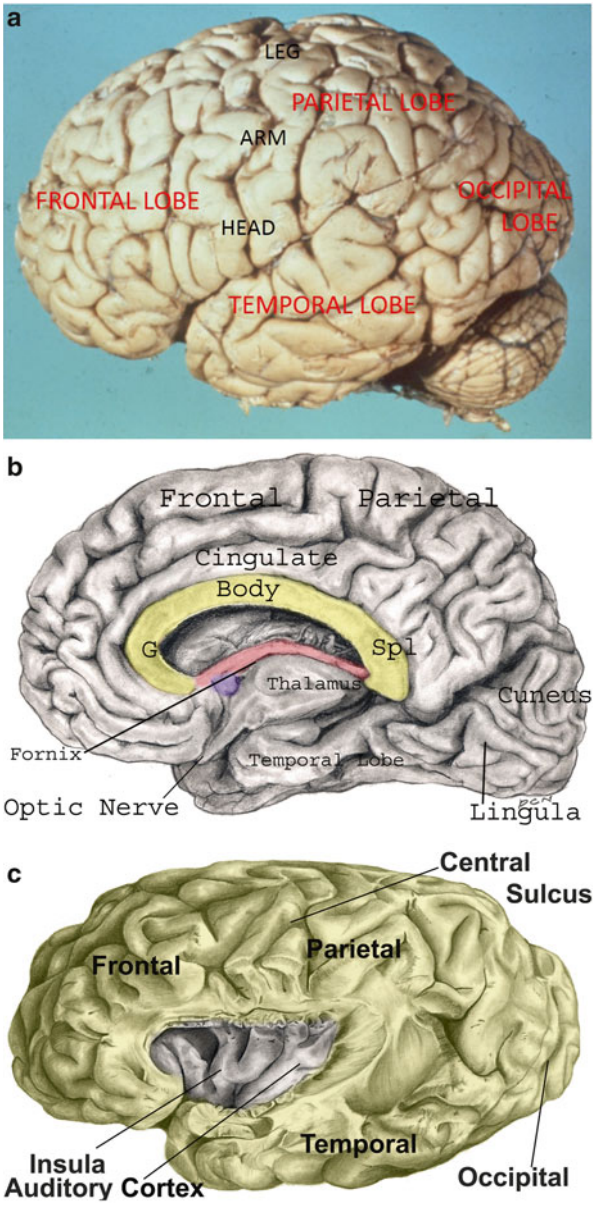

Fig. 2.1 Normal brain. (**a**) The lobes gyri and major sulci labeled in the frontal, parietal, occipital, and temporal gyri, and the motor strip identified on the lateral surface of the brain. (**b**) Medial surface with the corpus callosum, fornix, and gyri and cingulate sulci labeled and the gyri and sulci in the frontal, parietal, occipital and temporal lobe labeled. (**c**) Frontal and parietal operculum removed to reveal insular cortex and auditory cortex of temporal lobe (transverse temporal gyri). (From Jacobson and Marcus [17])

Case One: Cerebrovascular Accidents (CVA) (Figs. 2.2–2.4, Modified from Jacobson and Marcus 2003)

A 62 year old, Left-handed, untreated male with hypertension had an infarct in the territory of the middle cerebral artery on the left after carotid clamping for removal of plaque in the left common carotid. The patient progressed from a weakness of the right hand to complete right hemiparesis with right central facial weakness and a mixed aphasia. There was a subsequent recovery in the right lower extremity. Figure 2.2 is the post mortem examination of the brain of Patient One showing an infarct in the right operculum of the precentral gyrus and insula.

Figure 2.3a is an MRI which shows the appearance of a normal patient at the level of the frontal operculum, while Fig. 2.3b is an MRI which shows an infarct in the cortical territory of the left superior branch of the middle cerebral artery in the frontal lobe with similar neurological findings to Case One.

Figure 2.4 is a micrograph which demonstrates a lesion in the right medullary pyramid several years after a lesion in the medial most portion of the left motor strip with resultant atrophy of the corticospinal pathway and resultant upper motor deficit with increased reflexes, weakness of movements and some disuse atrophy of the right lower leg.

Although cardiac disease is still the most common causes of death in middle and upper income countries, there have been improvements due to better nutritional choices, exercise, stopping smoking, reducing salt intake and taking of medicine

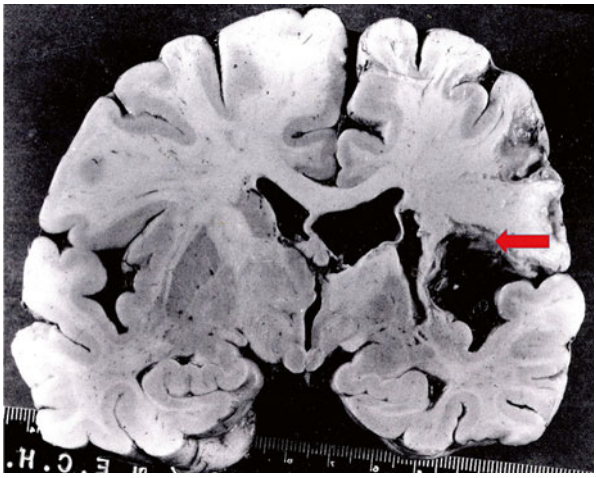

Fig. 2.2 CVA. This is a post mortem examination of the brain of Case One with a CVA showing an infarct in the left operculum of the precentral gyrus and insula (From Jacobson and Marcus [17])

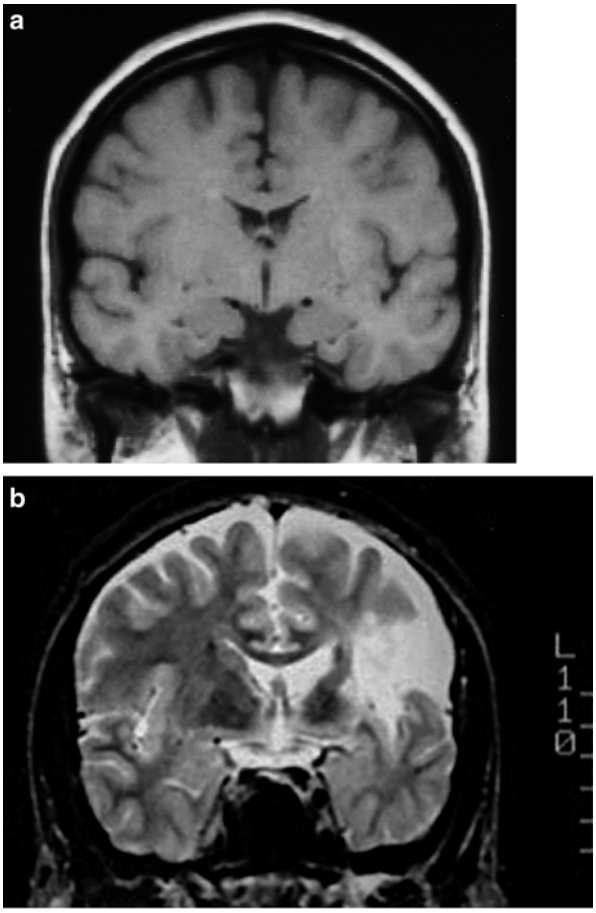

Fig. 2.3 CVA. (**a**) is an MRI which shows the appearance of a normal patient at the level of the frontal operculum, while (**b**) is an MRI which shows an infarct in the cortical territory of the left superior branch of the middle cerebral artery in the frontal lobe with similar neurological findings to Case One (From Jacobson and Marcus [17])

which will reduce the blood pressure. In lower income countries as shown in a recent article in Neurology [18] there is a critical need to alleviate the effects of hypertension, by encouraging life style changes, and reducing salt intake and when necessary treating patients with the inexpensive anti hypertensives (thiazides). The National Institute of Neurological Disease and Stroke of the National Institute of Health is dedicated to the eradication and treatment of stroke in the USA and the world www.ninds.nih.

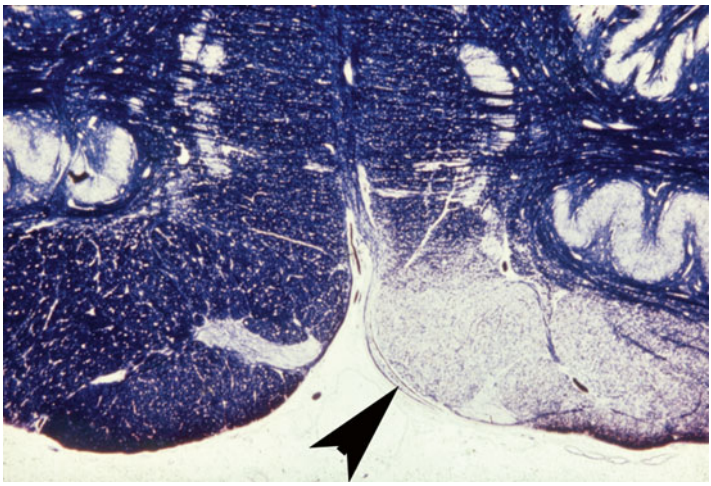

Fig. 2.4 CVA. This micrograph demonstrates a lesion in the right medullary pyramid several years after a lesion in the medial most portion of the left motor strip (controls the contralateral foot). This patient demonstrated atrophy of the corticospinal pathway and clinically demonstrated an upper motor deficit with increased reflexes, weakness of movements and some disuse atrophy of the right lower leg (From Jacobson and Marcus [17])

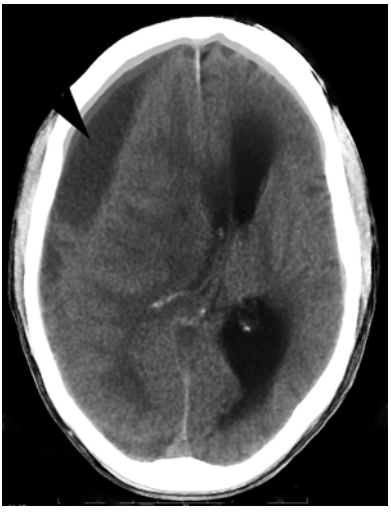

Fig. 2.5 Malaria. This CT is from a patient with a subdural hematoma and a displacement of the midline and compression of the lateral ventricles on cerebral malaria (From Kampala Imaging Center, courtesy of Dr. Rosemary Byanyima)

Group Two: Communicable Diseases, Malaria and HIV/AIDS

Case Two: Cerebral Malaria, Case developed by Dr. Erisa Mwaka Sabakaki, Fig. 2.5

A 32-year-old man presented with a history of fever, chills and weakness for 2 weeks along with generalized tonic-clonic seizures, occurring 2–3 times per day, for 5 days. He also had a history of loss of consciousness 2–3 times a day, each

episode lasting for 2–3 min. He complained of loss of power in the right upper limb for 4 days. He had had 4–5 episodes of severe vomiting during the duration of the illness. CNS examination revealed that he was conscious and oriented. There was no neck rigidity. Power in the right upper limb was 4/5. His sensory and motor systems were normal; there was no cranial nerve deficit. The other systemic examinations were normal. Biochemical and hematological investigations were normal. Peripheral smear for malarial parasite was positive and the patient was started on antimalarial drugs. CT of the brain revealed an irregular lesion, mixed hyper- and hypodense areas in the left high posterior frontoparietal region and the evidence of a subdural and subarachnoid hematoma in left frontoparietal region with surrounding hypodensity. Two days later, the patient complained of pain and swelling in the left lower limb. Venous Doppler of the limb showed deep vein thrombosis. The patient was treated aggressively with antithrombotics, antibiotics, antipyretics and anti-inflammatory drugs along with antacids. The patient completed the course of antimalarial drugs. He improved clinically. Follow-up CT scan of the brain done 1 month later showed a resolving infarct in the left frontoparietal region.

Figure 2.5 is a CT of a patient demonstrating a large subdural (arrow) external to the frontal lobe with a shift of the midline and the compression of the lateral ventricles on the right and enlargement of the ventricles on the left due to the presence of the *f. plasmodium* parasites in the subdural space and also in the adjacent parenchyma of the infected brain. It has been noted that the parasites sequester in cerebral capillaries and also produce additional intra- and perivascular pathology with retinopathy being very common [19, 20]. Malaria is caused by a bite from an infected female *anopheles* mosquito carrying the protozoan parasites of *falciparum plasmodium*. It affects over 650,000,000 people infected each year and causes 10 % of the deaths in the lower income countries including Uganda (1–3,000,000/year; [5]). It also is a major cause of poverty and hinders economic growth. There has been some progress in protecting children by providing mosquito nets but more help is needed, and there has been some progress in developing a vaccine. We have developed a video (Cerebral malaria, www.braindementia.org) from a case of Cerebral Malaria which demonstrates cortical atrophy, a subdural haematoma and dilation of the ventricles, a common finding in Malaria (www.cdc.gov/malaria).

Case Three: HIV/AIDS (Fig. 2.6)

A 38 year old female presented with left sided hemiplegia and weakness on the right side and dementia (Fig. 2.6). She has recently started on antiretroviral therapy with some success. Her CD4 was 455 cells/mm. The CT images shows lesions on the right (1) and left (3) rostral internal capsule and a lesion in the insular cortex on the right (3) all of which were consistent with HIV infection in the brain [21, 22]. These pathological findings are consistent with other studies that have shown similar infarcts due to HIV-associated *toxoplasmosis, tuberculosis* and *cryptococcosis* whose presence were not tested for in this patient. Our findings of dementia in this patient were supported by the brain atrophy which was noted with the widening of the sulci in the young woman. Poor care of patients with limitations in extensive investigations is not uncommon in LIMC settings. The cause of HIV is well documented. There is still no cure for HIV. There is antiretroviral medication which slows

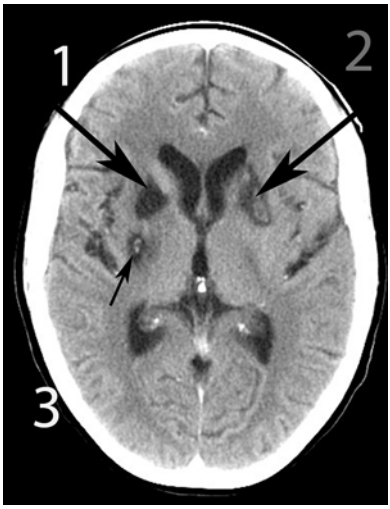

Fig. 2.6 HIV. This CT image of the brain is from Case Three. A 38 year old female presented with left sided hemiplegia and weakness on the right side and dementia. The CT images shows infarcts on the right (*1*) and left (*2*) in the rostral internal capsule and an infarct in the insula cortex on the right (*3*) due to the HIV infection. There is also significant evidence of brain atrophy with the widening of the sulci in this young woman (From the Kampala Imaging Center, courtesy of Dr. Rosemary Byanyima)

the progression from HIV to AIDS, and it can keep many people healthy for many years. However, these medicines are not widely available in poor countries. There are many groups working on developing a vaccine for HIV/AIDS and they have not yet succeeded, but there is a sense of optimism that there will be a vaccine 1 day.

Uganda is often held up as a model for Africa in the fight against HIV and AIDS [23, 24]. In Africa in most cases, HIV is spread heterosexually. Other causes include mother-to-child transmission, transfusion with infected blood or sharing needles in intravenous drug use. There are an estimated 1.2 million people living with HIV in Uganda, which includes 150,000 children. Strong government leadership, broad-based partnerships and effective and extensive public education campaigns using bill boards, newspapers, the radio, TV and internet are all contributing to a decline in the number of people living with HIV and AIDS. Uganda's success story must not detract from the consequences that AIDS continues to have across the country. An estimated 64,000 people died from AIDS in 2009 and over one million children have been orphaned by this devastating epidemic. The CDC has a very active surveillance and information upon the treatment of HIV (http://www.cdc.gov/hiv/topics/surveillance/) as does the WHO (http://www.who.int/hiv/en.)

Group Three (NCD) Neurodegenerative Diseases

Case Four: Alzheimer's Disease (AD) (Figs. 2.7 and 2.8)
A 64 year old male over the last 4 years had been having problems at work including inappropriate behavior, dress and memory problems. His changes in appearance and behavioral abnormalities including threatening his wife led him to be institutionalized by his family which was a very difficult experience for his wife and children

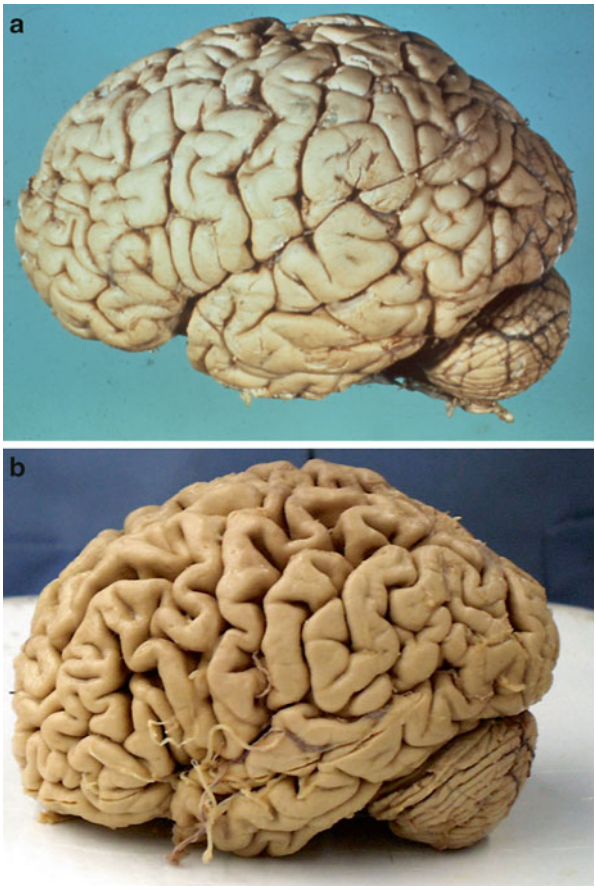

Fig. 2.7 (**a**) is the control, while (**b**) is from a patient diagnosed with Alzheimers' disease. In (**b**) from the patient with A Dnote the wide sulci throughout the brain which are a mark of extensive neuronal dropout. Compare the brain in (**b**) to that in Fig. 2.9b with frontotemporal degeneration (Courtesy of Dr. Stanley Jacobson)

(case developed by Drs. E. M Marcus and Stanley Jacobson). In Fig. 2.7a we show the appearance of a control brain while in Fig. 2.7b we show a brain from a patient diagnosed with Alzheimer's Disease showing major widening of the sulci throughout the brain due to the decrease in cortical gray matter/gyri which is the major pathology seen with this disease. In Fig. 2.8a we have included an MRI from a patient without AD at age 91 with a normal appearing hippocampus while in comparison we have included the MRI from a 71 year old male with severe AD. Figure 2.8b is from a 76 year old patient defined clinically as having AD and it shows severe atrophy of the hippocampus (from Marcus and Jacobson [25]). Please note that there is also atrophy in the hippocampus of the patients with AD enlargement of the ventricle due to the degeneration of the brain.

Alzheimer's disease is the most common cause of dementia and is a silent epidemic in US and much of the middle and upper income regions of the world. In the US there are over 5,000,000 affected individuals and it has deleterious effects on the personal and financial lives of the affected families. We were most fortunate at the

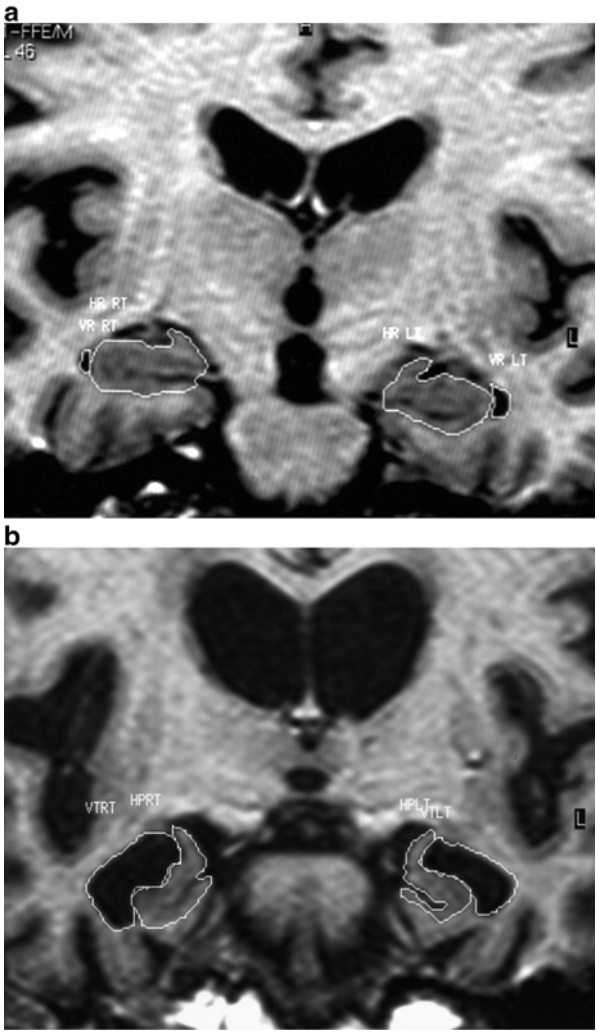

Fig. 2.8 Alzheimers' disease, MRI. In (**a**) we have include an MRI from a 91 year old male patient without AD at 91 with a normal appearing hippocampus; in (**b**) we have included the MRI from a 71 year old male with severe atrophy of the hippocampus (From Marcus and Jacobson [25]). Concomitant with the atrophy of the hippocampus there was an enlargement of the ventricular system due to the degeneration of the brain (From Jacobson and Marcus [17])

Ugandan workshop on Brain Degenerative Diseases to have Drs. Lee, Trojanowski and Schellenberg who have made great strides in reducing the effect of AD and Dr. Jeffrey Griffiths who described the heavy impact on the family and society of the AD patients. The Alzheimer's Organization is very active in supporting research, and helping families with this disease cope with its effects on affected individuals and their family (www.alz.org).

Case Five: Frontotemporal Degeneration/Picks Disease (Fig. 2.9)
This case is from the Gross Anatomy Laboratory at Tufts University School of Medicine. The patient was an 89 year old male. Figure 2.8 shows a photograph of the base of his brain demonstrating bilateral atrophy in the temporal and frontal

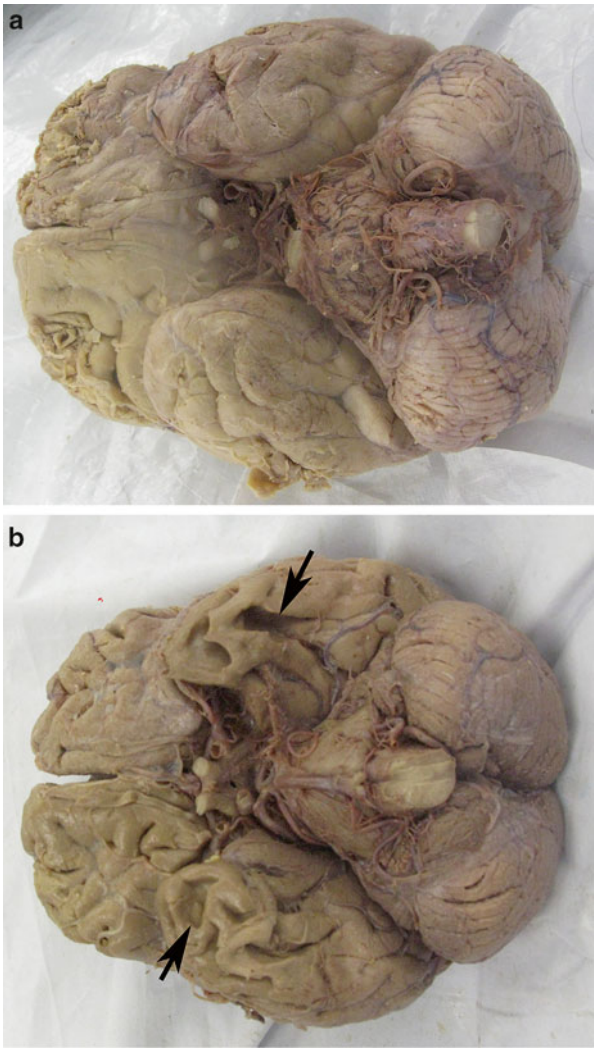

Fig. 2.9 Frontotemporal degeneration, Picks' disease. (**a**) The control brain. (**b**) The brain of this 89 year old male who demonstrated bilateral marked atrophy in the basal temporal and frontal lobes (*arrow*) with dementia and memory dysfunction which are the sign of this disease. The hippocampus was also atrophic (Courtesy of Dr. Stanley Jacobson)

lobes which also involved the hippocampus. He had changes in personality, language and memory. The hippocampus was atrophic [17]. This disease is similar to AD, but the regions in the brain that demonstrate atrophic degenerative changes are limited to the frontal and temporal lobes of the brain's regions. The Association for Frontotemporal Dementia is dedicated to treatment and control of this disease (www.theaftd.org).

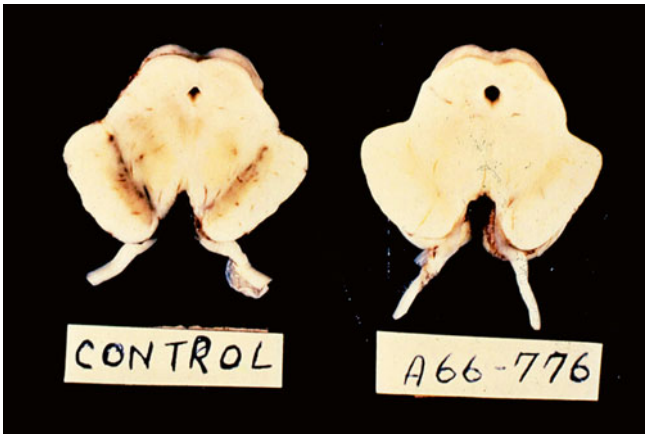

Fig. 2.10 Parkinson's disease. Note the normal appearance of the pigment in the substantia nigra of a 70 year old patient without disease (*left*), versus the marked loss of pigmentation in the substantia nigra pars compacta (*right*) (From Jacobson and Marcus [17]. Courtesy of Dr. Thomas Smith University of Massachusetts Department of Neurology)

Case Six: Parkinson's' Disease (Fig. 2.10, Modified from Marcus and Jacobson [25])

A 50 year old male developed a sense of fatigue and stiffness and lack of control of his left arm. He had a problem in writing and moving his leg. He said "I have to remember to lift it". When he walked there was a tendency to turn en bloc and there was decreased swinging of the arm. Over a period of a year he developed progression of the disease with cogwheel rigidity and micrographia with a pill rolling tremor at rest. Over the last 10 years he has undergone several different treatment regimens but the disease is still progressing with tremor at rest and rigidity and a slowly progressing dementia. There has been some discussion of whether he is a candidate for deep brain stimulation to stop the progression of the disease.

Parkinson's disease is the most common disease involving the basal ganglia (caudate, putamen and globus pallidus). The patient usually has several movement problems including a difficulty in walking, getting dressed, tying one's shoes, a tremor at rest and they may also develop dementia. They have a slow shuffling gait. The pathogenesis is the progressive loss of dopamine producing neurons in the pars compacta of the substantia nigra (Fig. 2.10). Figure 2.10A shows the normal appearance of the substantia nigra in a 70 year old patient without disease while in Fig. 2.10B shows the marked loss of pigmentation in the substantia nigra pars compacta in a patient with PD. In normal aging the rate of cell loss in the substantia nigra is 4 % per decade while in the PD patient it is about 45 % per decade. In the United State there are approximately 1,000,000 patients with the disease. Recently Drs. Lee and Trojanowski and colleagues [26, 27] have made great strides in understanding the basis of PD by determining that the transmission of a pathological α-synuclein gene initiates Parkinson-like neurodegeneration in transgenic mice.

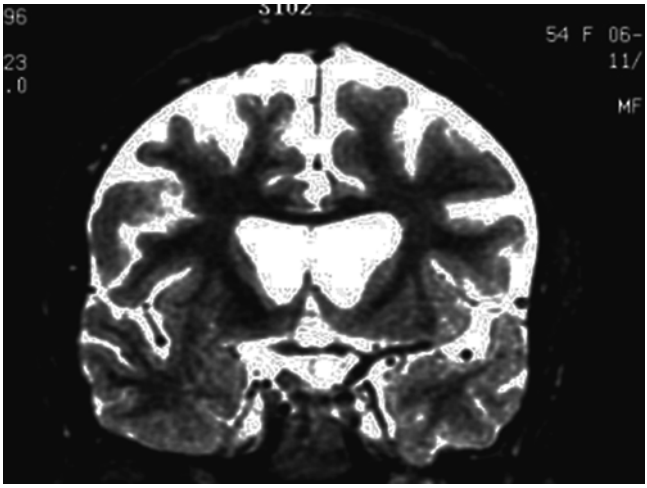

Fig. 2.11 This MRI is from 50 year old female patient who for several years had been noted to be nervous and had many restless movements. Her family felt that recently she was not thinking as clearly and had been undergoing a personality change (From Jacobson and Marcus [17])

This finding may lead to the development of an antibody to block this compound and mitigate the effects of PD. The Parkinson Organization (www.parkinson.org) website is a very helpful and describes this disease and the ongoing research aimed at the control and eradication of PD.

Case Seven: Huntington's' Disease [17] (Figs. 2.11–2.13)
A 50 year old female patient (Fig. 2.11) for several years had been noted to be nervous and had many restless movements. Her family felt that recently she was not thinking as clearly and had been undergoing a personality change. In addition, she demonstrated uncontrolled facial movements, including grimaces, head turning to shift eye position, and quick, sudden, sometimes wild jerking movements of the arms, legs, face and other body parts with restlessness and fidgeting. Additional behavioral changes may also occur in HD even before the movement problems. These can include: memory problems (dementia), behavioral disturbances, hallucinations, irritability, moodiness, paranoia and psychosis.

The MRI in Fig. 2.12a is from a normal patient while Fig. 2.12b is from a 45 year old patient with HD and shows enlarged ventricles and a thinning out of the cerebral cortex and basal ganglia especially noted in the rostral regions of the diencephalon around the anterior limb of the internal capsule. Patients with HD have enlarging of the ventricles, called "box car ventricles' and the thinning out of the basal ganglia. Figure 2.13 is the postmortem picture of the brain from a patient with HD with marked atrophy in the caudate and putamen with a dilation of the lateral ventricles. In this case there was the noted less involvement of the cerebral cortex.

Modern genetic analysis using recombinant DNA techniques has shown a defect in the short arm of chromosome 4 in patients with HD. The defect causes a part of DNA, called a CAG repeat, to occur many more times than it is supposed to.

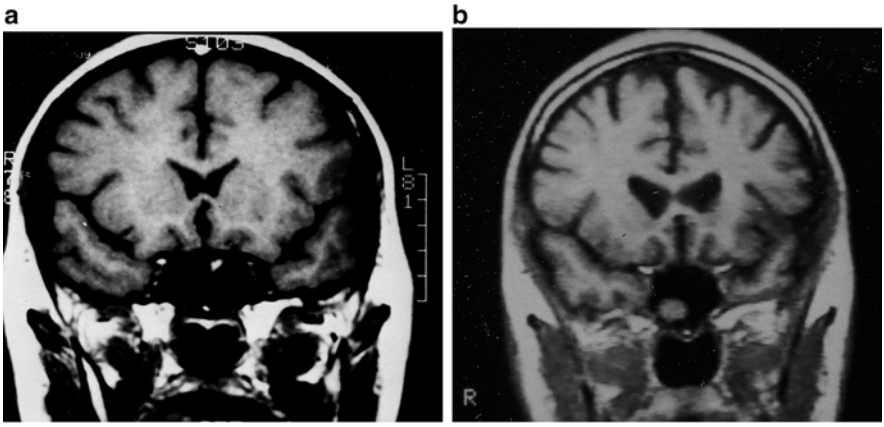

Fig. 2.12 Huntington's disease. (**a**) is from a normal patient in the mid-frontal region. (**b**) is from a 45 year old. patient with HD and shows a marked atrophy of the cerebral cortex and of the caudate nucleus in this patient with a familial history of the disorder and a significant increase in the CAG nucleotide repeats there is a thinning out of the cerebral cortex and basal ganglia especially noted in the rostral regions of the diencephalon around the anterior limb of the internal capsule. This patient with HD has enlarged ventricles, called "box car ventricles' and the thinning out of the basal ganglia (From Jacobson and Marcus [17])

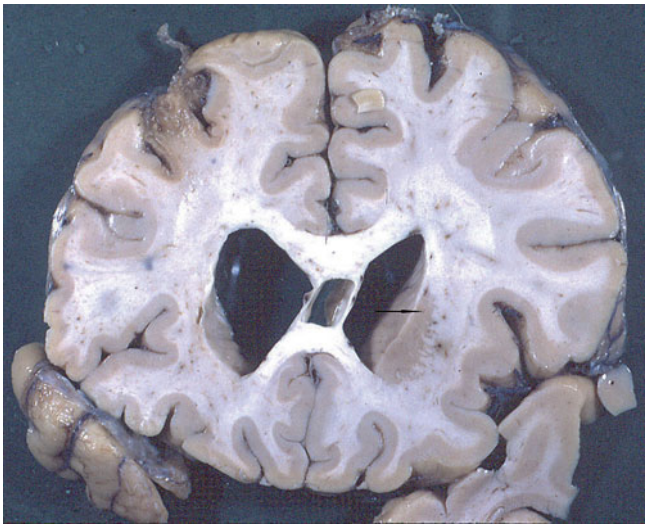

Fig. 2.13 A patient with Huntington's disease. There is marked atrophy in the caudate and putamen with a dilation of the lateral ventricles. In this case there was also less involvement of the cerebral cortex than the patient in Fig. 2.12 (Courtesy of Dr. Emanuel Ross)

Normally, this section of DNA is repeated 10–28 times. But in persons with Huntington's disease, it is repeated 36–120 times. As the gene is passed down through families, the number of repeats tends to get larger, especially where there is consanguinity. The larger the number of repeats, the greater are the chances of developing HD symptoms at an earlier age. Therefore, as the disease is passed along in families, symptoms develop at younger and younger ages. There are two forms of Huntington's disease. The most common is adult-onset Huntington's disease. Persons with this form usually develop symptoms in their mid-30s and 40s. An early-onset form of Huntington's disease accounts for a small number of cases and begins in childhood or adolescence. If one of the parents has Huntington's disease, there is a 50 % chance of getting the gene for the disease. If one gets the gene from one's parents, they will develop the disease at some point in your life, and can pass it onto their children [28]. Inheritance is autosomal dominant. There are, currently, no known methods to reverse the course of this disease, consequently current interventions focus on easing the burden of care on the affected patient and their family and genetic counseling (*Huntington's Disease Society of America*; www.hdsa.org).

Case Eight: Amyotrophic Lateral Sclerosis, ALS (Figs. 2.14 and 2.15)
Case W was a 66 year old man who originally presented for medical evaluation with a history of progressively increasing generalized muscle weakness involving both the upper and lower extremities. He initially noted weakness of his right hand manifested as difficulty with fine motor skills such as writing or buttoning a shirt or coat. He also noted a tendency to drop things when holding objects with the right hand. He subsequently noted lower extremity weakness involving proximal (thigh) muscles. He had difficulty rising from a chair and walking up stairs. He developed distal muscle weakness manifested as a foot drop, the so called "slapping" gait. Several months later, he developed dysarthria (slurring of speech) and dysphagia (difficulty swallowing) especially for thin liquids. This got progressively worse so that in the 2 weeks before admission to the hospital he frequently experienced choking and coughing when drinking liquids. At the time of admission the patient had significant cough, fever and dyspnea. On physical examination he had tachypnea with a respiratory rate of 24 breaths per minute. Chest exam revealed crackles at both bases. He was found to have significant hypoxemia. The patient's dysphagia (from bulbar muscle involvement) predisposed him to aspiration and hence pneumonia. His presentation of cough, fever, dyspnea, with crackles on physical examination was consistent with this diagnosis. This case was developed into a virtual patient by Drs. Scott Epstein, EM Marcus, Samuel Giles, and Stanley Jacobson to illustrate the deleterious effects of ALS and the illustrated brain is from the patient with ALS from the gross lab at Tufts University in Fig. 2.14. The brain shows atrophy bilaterally of the precentral and post central gyrus, premotor, and prefrontal cortex, but especially notable bilaterally is the motor strip which is very thin and has been called "razor thin" and with the resultant widening of the adjacent sulci. Compare this brain

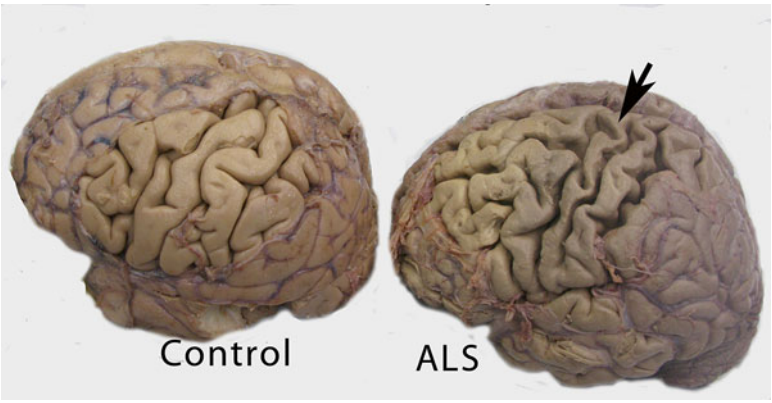

Fig. 2.14 ALS. Photograph of a brain on the *left* from a 70 year old patient without disease in the brain while the brain on the *right* is from a 66 year old patient, Case W, with ALS. The brain from the ALS patient shows atrophy of the precentral (*arrow*) and post central gyrus, premotor, and prefrontal cortex but especially notable bilaterally in the motor strip (*arrow*) which is very thin and has been called "razor thin"-compare to the brain from a 70 year old male who died of cancer (Courtesy of Dr. Stanley Jacobson)

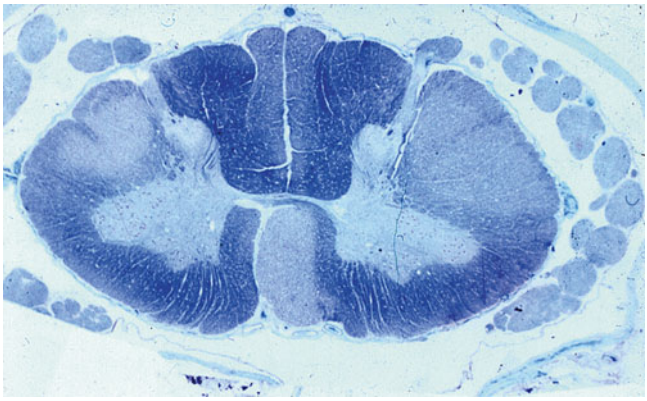

Fig. 2.15 A micrograph that shows the pattern of degeneration in the cervical spinal cord of a patient with ALS demonstrating degeneration bilaterally in the lateral corticospinal tract and in the anterior corticospinal tract on the left (From Jacobson and Marcus [17]. Courtesy of Dr. Jose Segarra)

from the patient with ALS to the control brain from a 70 year old who died of cancer. The atrophy in the prefrontal and post central gyrus, in addition to the precentral/motor cortex, produces degeneration in the upper motor neurons that form the corticospinal and corticobulbar pathways which originate from these cortical regions.

Figure 2.15 is a micrograph that shows the pattern of degeneration in the spinal cord of a patient with ALS in the motor, premotor and prefrontal cortices demonstrating degeneration in the lateral and anterior corticospinal tract. There was also degeneration of the lower motor neurons in the Ventral Horn Cells. There are about

20,000 people in the United States with this disease today where the disease is commonly linked to a famous baseball player, Lou Gehrig, who died from it in the 1930s hence Lou Gehrig's disease. Recently there have been major strides in understanding the underlying cause and prolonging the life of patients who come down with this disease but there is yet no cure insight. The deleterious effects of ALS and the ongoing research on this disease are well illustrated by the ALS Society of the US (www.als.org).

Conclusion

In this paper we have reviewed many of the anatomical and clinical features seen in the brain caused by the Communicable Diseases of malaria and HIV/AIDS, and the Non-Communicable Diseases including CVA/strokes and the neurodegenerative diseases of AD, PD, HD and ALS. We have also discussed the major strides made in reducing the effects of CVAs and malaria on the brain. We have discussed the effects on the families of the affected patients who presented with the neurodegenerative diseases of AD, PD, HD, and ALS. Finally, we have reported on the major strides made in dealing with the deleterious effects of these disease on the brain matter. Other chapters in this book have discussed the effects of HIV/AIDS, malaria, nutritional deficiencies on the brain.

Acknowledgements We want to thank Dr. Erisa Mwaka Sabakaki of the Department of Anatomy of the College of Health Sciences of Makerere University who developed the case of Cerebral Malaria we used in this paper. We are indebted to Stephen Ocaya for the development and maintenance of the website braindementia.org that was used during the meeting and is still up and running and is where the video on Malaria is stored. We want to thank Dixkson Muyomba for scanning the case files from Mulago Hospital Department of Radiology and Craig Wambura for downloading all the images from the Kampala Imaging Center.

References

1. Tattersall I. Human origins: out of Africa. Proc Natl Acad Sci. 2009;106:16018–21.
2. Moreno E. The society of our "out of Africa" ancestors. The migrant warriors that colonized the world. Commun Integr Biol. 2011;4, J Urban Health. Suppl 2:256–65.
3. Johanson DC. Lucy (*Australopithecus afarensis*). In: Ruse M, Travis J, editors. Evolution: the first four billion years. Cambridge, MA: The Belknap Press of Harvard University Press; 2009. p. 693–7.
4. Johanson C, Wong K. Lucy's legacy: the quest for human origins. New York: Harmony Books; 2009.
5. World Health Organization, WHO, Data and Statistics, 2011.
6. Center for Disease Control (CDC). Leading causes of death in the United States Centers for Disease Control and Prevention. US Government, Washington DC. 2011.
7. Jamison DT, Feachem RG, Malegapuru A, Makgoba W, Bos ER, Baingana FK, Hofman KJ, Khama O. Disease and mortality in sub-Saharan Africa. 2nd ed. Washington, DC: World Bank; 2006.

8. Samuel JC, Sankhulani E, Qureshi JS, Baloyi P, Thupi C, et al. Under-reporting of road traffic mortality in developing countries: application of a capture-recapture statistical model to refine mortality estimates. PLoS ONE. 2012;7(2):7–11.
9. Ziraba AK, Kyobutungi C, Zulu EM. Fatal injuries in the slums of Nairobi and their risk factors: results from a matched case-control study. PLoS Med. 2011;2:163–70.
10. Love S, Louis DN, Ellison DW. Greenfield's neuropathology. 8th ed. London: Edward Arnold (Publishers) Limited; 2008.
11. Victor and Roper. Principles of neurology. 2008; 8th ed, McGraw-Hill, NY, 2014.
12. Lagarde E. Road traffic injury is an escalating burden in sub-Sahara Africa. PLoS Med. 2007;4:170–75.
13. Health Insurance and Portability Act, nih.US gov/hipaa/1996.
14. Virtual Patient Special Issue. Medical Teacher, vol 31. 2009.
15. Ellaway RH, Poulton T, Smothers V, Greene P. Virtual patients come of age. Med Teach. 2009;31(8):683–4.
16. Jacobson S, Epstein SK, Albright S, Ochieng J, Griffiths J, Coppersmith V, Polak JF. Creation of virtual patients from CT images of cadavers to enhance integration of clinical and basic science student learning in anatomy. Med Teach. 2009;31(8):749–51.
17. Jacobson S, Marcus EM. Neuroanatomy for the neuroscientist, 2nd ed. Springer. New York, 2011.
18. Chin JH. Stroke in Sub-Saharan Africa: an urgent call for prevention. Neurology. 2012;78:1007–8.
19. Cordoliani YS, Sarrazin JL, Felten D, Caumes E, Lévêque C, Fisch A. MRI of cerebral malaria. Am J Neuroradiol. 1998;19:871–4.
20. Taylor TE, Wenjiang JF, Carr RA, Richard O, Whitten RO, Mueller JG, Fosiko NG, Lewallen S, Liomba NG, Molyneux EM. Differentiating the pathologies of cerebral malaria by *postmortem* parasite counts. Nat Med. 2004;10:143–5.
21. Quinn TC. Epidemiology of human immunodeficiency virus infection and acquired immunodeficiency syndrome. In: Goldman L, Schafer A, editors. Cecil medicine. 24th ed. Philadelphia: Saunders Elsevier; 2011. Chap. 392.
22. Sterling TR, Chaisson RE. General clinical manifestations of human immunodeficiency virus infection (including the acute retroviral syndrome and oral, cutaneous, renal, ocular, metabolic, and cardiac diseases). In: Mandell GL, Bennett JE, Dolin R, editors. Principles and practice of infectious diseases. 7th ed. Philadelphia: Elsevier Churchill Livingstone; 2009. Chap. 121.
23. Genuis SJ, Genuis SK. AIDS prevention in Uganda why it has worked. Postgrad Med J. 2005;81:615–7.
24. Uganda Reverses the tide of AIDS, WHO, Data and Statistics 1998.
25. Marcus EM, Jacobson S. Integrated neurosciences a clinical problem solving approach. Boston: Kluwer; 2003.
26. Irwin DJ, Abrams JY, Schonberger LB, Leschek EW, Mills JL, Lee VM, Trojanowski JQ. Evaluation of potential infectivity of Alzheimer and Parkinson disease proteins in recipients of cadaver-derived human growth hormone. JAMA Neurol. 2013;70:462–8.
27. Luk KC, Kehm V, Carroll J, Zhang B, O'Brien P, Trojanowski JQ, Lee VM. Pathological α-synuclein transmission initiates Parkinson-like neurodegeneration in nontransgenic mice. Science. 2012;338:949–53.
28. NIMH. Top research advances NIMH, NIH, gov.; 2011.

Chapter 3
A 24-Hour Walk Through Mulago National Referral Hospital, Uganda: What Kind of In-Patients Do You See?

Nazarius Mbona Tumwesigye, Jacinto Amandua, David Lubogo, and Victoria Masembe

Abstract Mulago hospital is the final general National Referral Hospital (NRH) in Uganda, and having one such hospital is not unusual in many Low and Middle Income Countries. Mulago hospital, as the nation's referral facility has a bed capacity of 1,790 but frequently the number of inpatients exceeds the available beds, hence creating floor cases. Social demographic characteristics of patients and reasons for hospitalization are not well documented and the reasons for the hospital's congestion are not clear but may be related to the relative lack of other general hospital facilities in the city. The country is currently in the process of decongesting the hospital.

To better inform the decongestion process, a census of all inpatients in the NRH was carried out over 24 h starting early morning of 14th July, 2011. One hundred eighteen health workers, who were mostly nurses and midwives, were consecutively selected and trained for data collection. Some data collectors worked during the day and others during the night. The main tool used for data collection was a transcription form on which all data from the patient files were recorded. All data were entered in epidata v3 software and exported to STATA v10. Descriptive statistics involving population pyramid and cross-tabulations were used to present the profile of the in-patients.

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S. Musisi, S. Jacobson (eds.), *Brain Degeneration and Dementia in Sub-Saharan Africa*, DOI 10.1007/978-1-4939-2456-1_3

The total number of inpatients in Mulago national referral hospital was 1,763 at the time of the survey. The majority of the patients were female (60 %), youth (15–24 years) [40 %] or under-fives (<5 years) [18 %], from Kampala city and Wakiso district (64 %), had attained at least primary level of education (53 %) but were unemployed/low income earners (54 %). Of the patients seen, 29 % were admitted on the surgical ward, 25 % on obstetrics and gynecology ward, 20 % on the medical ward, 18 % on the pediatric ward, 5 % on the cancer institute and 1 % on the psychiatric ward. Very few inpatients (8, 0.5 %) were from outside the country. These results add more support for the need to decongest the national referral hospital e.g. by building other general hospital facilities in the city.

Keywords Mulago Hospital National Referral Hospital • In patient survey • Surgical ward • Obstetrics and gynecology ward • Medical wards • Pediatric ward • Cancer institute • Psychiatric ward

Introduction

Mulago Hospital was founded in 1913 by Albert Ruskin Cook [1] and it started as a Sexually Transmitted Disease and Trypanosomiasis treatment centre. The new and main part of the hospital was completed in 1962, at the time of the country's independence. It has 1,790 beds and runs on an annual budget of UShs 56.8 billion (US$22.7 million) [2] which is far below the amount required for full functioning. The government budgetary allocation to the health sector is, on average, 9.6 % of the total government budget [3] and Mulago hospital alone consumes approximately 12 % of it [2]. On a daily basis the hospital receives 6,000–7,000 outpatients and 2,000–3,000 inpatients per day (Executive Director Mulago Hospital, 21 May 2014, State of Mulago Hospital, Personal communication, Kampala). In terms of staffing, the hospital has 87 % of its approved posts (2,423/2,801) filled by the health workers [4]. The Hospital is a University teaching hospital and offers comprehensive specialist clinical services that include psychiatry, Ear, Nose and Throat (ENT), ophthalmology, higher level surgical and medical services, general medical services, pediatric and clinical support services (laboratory, medical imaging, pathology), as well as conducting health research [3]. Of note is that up to today (2014), the hospital has no geriatric medicine service, despite an increasing population of people aged 60 years and above. The Administration of the hospital runs through seven directorates namely: Medical, surgical, diagnostics, obstetrics and gynecology, pediatrics and child health, finance and administration, as well as Private patients services.

The patient demand for specialist services at most referral facilities in Africa greatly varies depending on whether a particular service is available at the health facility in their neighborhood. For instance, a study carried out at Muhimbili referral hospital in Tanzania found that of all the patients who presented at the referral facility, the (36.8 %) sought for surgical services, followed by obstetrics and gynecology

services (29.9 %), general medicine (18.9 %), pediatric and neonatal services (9.4). Only 3.5 % sought psychiatric services, while 1.5 % sought other services [5]. Some patients also presented to the referral facility simply because the facility was the one nearest to them, instead of visiting lower level facilities where their conditions could easily be managed. This contributes to unnecessary congestion and inappropriate use of referral facilities [5, 6].

The immediate catchment population of Mulago hospital is estimated at three million people (9.4 % of national population) in Kampala city and neighboring districts while the wider catchment population is the nation's estimated 35.4 million people [7]. At the current national population growth rate of 3.2 % and 5.6 % for Kampala city the catchment population is bound to increase considerably [7, 8]. The government and Kampala Capital City Authority (KCCA) have started implementing plans to decongest the hospital and already one large hospital has been constructed at Nagulu 4 km away from Mulago NRH. Information on the kind of patients which Mulago hospital admits is, however, very scanty yet it would guide on the nature and capacity needed for the new health infrastructural developments in the city and neighboring districts. This paper provides a socio-demographic description of the in-patients currently seen at the hospital.

Methods

A 24 h census of all in-patients at Mulago national referral hospital was carried out starting at 8 am of the 14th of July and ended at 8 am of 15th July 2010. The main objective of the census was to determine the prevalence of life limiting illnesses at the hospital but this paper re-analyses the data to focus on description of the patients. The main method of data collection was record review using a standardized transcription form on which all information from the patient file was recorded. All wards were visited. One hundred eighteen health workers, mostly nurses and midwives, were selected and trained for data collection. The data collectors worked in shifts. Information was collected on the patient's records and through observations. It included demographic and social characteristics, area of residence, attendants and date and time of admission. All data collected were entered in epidata V3 software whose data entry screen had been fitted with range and consistency checks. The data were exported to STATA V12 for analysis which involved basic frequency and cross-tabulations.

Results

General Description

Overall, there were 1,763 inpatients from the existing 40 wards in the hospital at the time of the survey giving a bed occupancy rate of 98.5 %. Of the 1,763 patients, 29 % were admitted on the surgical ward, 25.4 % to the obstetrics and Gynecology

ward, 20.2 % to the medical ward, 18 % to the pediatric ward, 5 % to the cancer institute, 1 % to both the psychiatric and heart institute (Fig. 3.1). The figure further shows that the commonest cause of admission among men were conditions that needed surgery while among women it was obstetrics and gynaecology (birthing) conditions. The next common cause of admission among males was paediatric related conditions while among females it was conditions that need surgery.

Figure 3.2 shows a population pyramid for patients in Mulago and the national population pyramid. While patients' age distribution is not expected to be the same distribution with the general population the figure is an important tool for description and discussion of in-patients. It is clear that under 5 s and women in middle ages were the most prevalent in-patients. Those aged 60 years and above were 10 % of the in-patients. Nationally the proportion aged 60 years and above is 2.5 % [9].

Table 3.1 shows general characteristics of the inpatients found in the hospital on the census day. Expectedly, close to a half (44 %) of the inpatients originated from Kampala city while 20 % come from Wakiso district which almost encircles Kampala. Other neighboring districts contribute 11 % while other districts contribute almost a quarter (24 %). Most of the in-patients were married (39 %) and this was more evident among women (44 %) than men (35 %). The number of divorced was 11 % and it was higher among women (14 %) than men (6 %). When the under 15 year olds and those missing information are deducted the proportion of the widowed/divorced becomes 15.5 %.

The most prevalence education attainment is primary level (36 %) and it was nearly the same for men and women. The next prevalent is secondary education. Education level was not applicable to 18 % of the inpatients because they were under 5 years old.

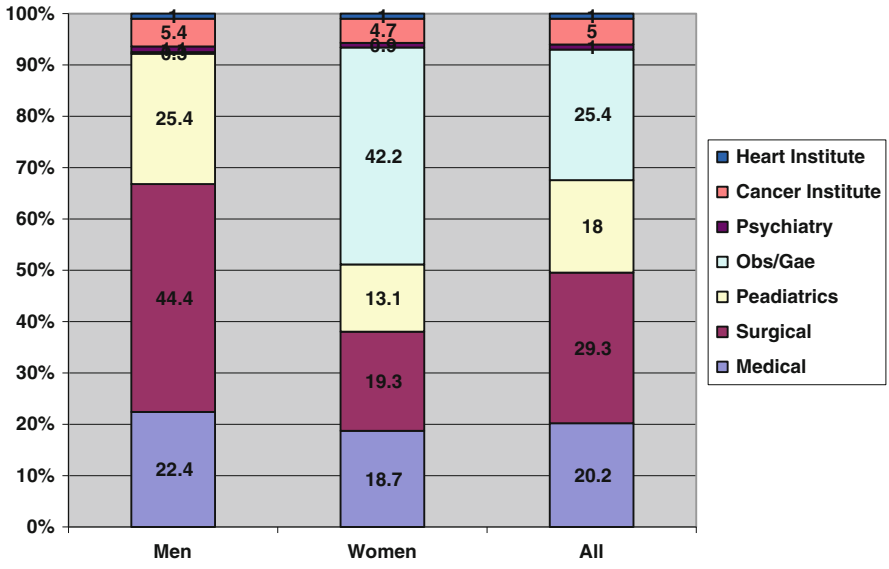

Fig. 3.1 Distribution of the in-patients by sex and ward

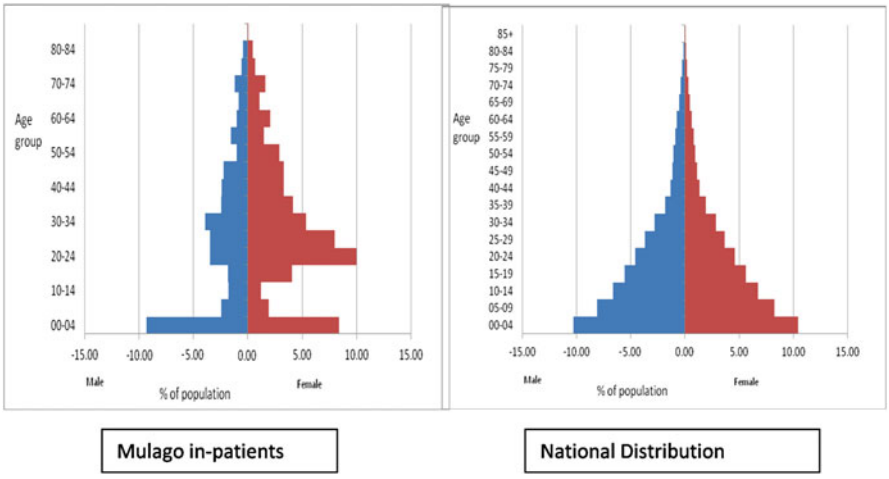

Fig. 3.2 Distribution of the inpatients by age and sex compared to the national distribution

The religious distribution of the in-patients reflected the country's picture in that all major religions were represented except that the level of representation differs. For example according to the 2001 national census Catholics were 41 % while Muslims were 15 %. During the study night at the NRH the Catholics were 33 % while Muslims were 22 %.

The occupation distribution showed high unemployment levels among these inpatients. Nearly a third (30 %) were not employed, 16 % were peasant farmers while those engaged in manual labour were nearly 9 %. Since manual labour and peasant farming are normally regarded as low paying employment this puts the prevalence of unemployed/low income inpatient at 54 %. When children under 15 those whose information is missing are left out the proportion of the unemployed/manual labour/peasant farmers rises to 74 %.

Ward Specific Descriptions

Table 3.2 shows the ward specific information. In this section the inpatients are described ward by ward.

Medical Wards

In the medical wards, females (57 %) were more than males (44 %) and it was dominated by people aged 25–55 years (60.2 %). The distribution by district shows most people were from either Kampala or Wakiso district (74 %). The majority were either married or single. Being from mainly urban area explains the relatively high proportion that had attained tertiary level education (12 %).

Table 3.1 Overall background characteristics of the in-patients by sex

Characteristics	Males	Female	All	Chi-sq test
Age group				
<5	163(23.2)	147(14.0)	310(17.6)	p<0.001
5–14	74(10.5)	55(5.2)	129(7.4)	
15–24	93(13.3)	246(23.4)	339(19.3)	
25–34	130(18.5)	234(22.2)	364(20.8)	
35–44	85(12.1)	131(12.5)	216(12.3)	
45–54	57(8.1)	109(10.4)	166(9.5)	
55+	100(14.3)	130(12.4)	230(13.1)	
District				
Wakiso	133(18.9)	220(20.8)	353(20.0)	p<0.001
Kampala	281(39.9)	501(47.4)	782(44.4)	
Neighboring districts	90(12.8)	101(9.6)	191(10.8)	
Other districts	199(28.2)	230(21.7)	429(24.3)	
Outside the country	2(0.3)	6(0.6)	8(0.5)	
Marital status				
Single	150(21.3)	183(17.3)	333(18.9)	p<0.001
Married	244(34.6)	438(41.4)	682(38.7)	
Divorced/widowed	41(5.8)	146(13.8)	187(10.6)	
Not applicable[a]	234(33.2)	202(19.1)	436(24.7)	
Missing information	36(5.1)	89(8.4)	125(7.1)	
Education				
None	64(9.1)	143(13.5)	207(11.7)	p<0.001
Primary	239(33.9)	381(36.0)	620(35.2)	
Secondary	149(21.1)	285(26.9)	434(24.6)	
Tertiary	69(9.8)	79(7.5)	148(8.4)	
Not applicable (<5 years)	162(23.0)	146(13.8)	308(17.5)	
Missing information	22(3.1)	24(2.3)	46(2.6)	
Religion				
Catholic	221(31.4)	357(33.7)	578(32.8)	P=0.178
Protestant	273(38.7)	366(34.6)	639(36.3)	
Moslem	154(21.8)	225(21.3)	379(21.5)	
Pentecostal	38 (5.4)	86(8.1)	124(7.0)	
Other Christian	15(2.1)	19(1.8)	34(1.9)	
Missing	4 (0.6)	5(0.5)	9(0.5)	
Occupation				
None	157(22.3)	367(34.7)	524(29.7)	p<0.001
Peasant farmer	106(15.0)	168(15.9)	274(15.5)	
Business	71(10.1)	113(10.7)	184(10.4)	
Manual labour	61(8.7)	91(8.6)	152(8.6)	
Formal employment	76(10.8)	76(7.2)	152(8.6)	
Not applicable[a]	208(29.5)	187(17.7)	395(22.4)	
Missing information	26(3.7)	56(5.3)	82(4.7)	
All	706(400.0)	1058(60.0)	1,763(100.0)	

[a] Mostly under 15 years

Table 3.2 Socio-demographic characteristics by major ward category

Characteristics	Medical	Surgical	Paed-iatrics	Obstetrics/ gynacol	Psychiatry	Cancer institute	Heart institute	All
Sex								
Male	158(44.4)	313(60.5)	179(56.3)	00	8(44.4)	38(43.2)	7(38.9)	705(40.0)
Female	198(55.6)	204(39.5)	139(43.7)	446(99.6)	10(55.6)	50(56.8)	11(61.1)	1058(60.0)
Age group								
<5	0(0.0)	47(9.2)	254(79.9)	0(0.0)	0(0.0)	2(2.3)	2(11.1)	310(17.7)
5–14	8(2.2)	42(8.2)	64(20.1)	3(0.7)	1(5.6)	16(18.2)	1(5.6)	129(7.5)
15–24	63(18.0)	83(16.2)	0(0.0)	175(39.1)	8(44.4)	9(10.2)	1(5.6)	339(19.3)
25–34	89(25.4)	115(22.4)	0(0.0)	145(32.4)	4(22.2)	9(10.2)	1(5.6)	364(20.8)
35–44	80(22.8)	64(12.5)	0(0.0)	58(13.0)	1(5.6)	11(12.5)	2(11.1)	216(12.3)
45–54	47(13.4)	57(11.1)	0(0.0)	36(8.0)	3(16.7)	18(20.5)	5(27.8)	166(9.5)
55+	64(18.2)	105(20.5)	0(0.0)	31(6.9)	1(5.6)	23(26.1)	6(33.3)	230(13.1)
District								
Wakiso	72(20.2)	80(15.5)	65(20.4)	123(27.5)	4(22.2)	6(6.8)	3(16.7)	353(20.0)
Kampala	191(53.7)	173(33.5)	182(57.2)	216(48.2)	7(38.9)	8(9.1)	5(27.8)	782(44.4)
Neighboring districts	34(9.6)	72(13.9)	35(11.0)	39(8.7)	3(16.7)	7(8.0)	1(5.6)	191(10.8)
Other districts	57(16.0)	188(36.4)	36(11.3)	68(15.2)	4(22.2)	67(76.1)	9(50.0)	429(24.3)
Other country	2(0.6)	4(0.8)	0(0.0)	2(0.5)	0(0.0)	0(0.0)	0(0.0)	8(0.5)
Marital status								
Single	104(29.1)	126(24.4)	7(2.2)	72(16.1)	10(55.6)	11(12.5)	4(22.2)	333(18.9)
Married	157(44.1)	204(39.5)	0(0.0)	278(62.1)	2(11.1)	32(36.4)	8(44.4)	682(38.7)
Divorced/widowed	64(18.0)	55(10.6)	0(0.0)	42(9.4)	3(16.7)	19(21.6)	4(22.2)	187(10.6)
Not applicable[a]	9(2.5)	85(16.4)	311(97.8)	10(2.2)	1(5.6)	18(20.5)	2(11.1)	436(24.7)
Missing information	22(6.2)	47(9.1)	0(0.0)	46(10.3)	2(11.1)	8(9.1)	0(0.0)	125(7.1)

(continued)

Table 3.2 (continued)

Characteristics	Medical	Surgical	Paed-iatrics	Obstetrics/ gynacol	Psychiatry	Cancer institute	Heart institute	All
Education								
None	45(12.6)	77(14.9)	19(6.0)	45(10.0)	0(0.0)	19(21.6)	2(11.1)	207(11.7)
Primary	151(42.4)	201(38.9)	42(13.2)	179(40.0)	4(22.2)	36(40.9)	7(38.9)	620(35.2)
Secondary	100(28.1)	127(24.6)	1(0.3)	177(39.5)	9(50.0)	15(17.1)	5(27.8)	434(24.6)
Tertiary	42(11.8)	54(10.4)	0(0.0)	37(8.3)	3(16.7)	10(11.4)	2(11.1)	148(8.4)
NA (<5years)	4(1.1)	46(8.9)	253(79.6)	1(0.2)	0(0.0)	2(2.3)	2(11.1)	308(17.5)
Missing information	14(3.9)	12(2.3)	3(0.9)	9(2.0)	2(11.1)	6(6.8)	0(0.0)	46(2.6)
Occupation								
None	120(33.7)	150(29.0)	5(1.6)	211(47.0)	11(61.1)	20(22.7)	7(38.9)	524(29.7)
Peasant farmer	61(17.1)	116(22.4)	0(0.0)	51(11.4)	1(5.6)	41(46.6)	4(22.2)	274(15.5)
Business	60(16.9)	61(11.8)	0(0.0)	53(11.8)	2(11.1)	5(5.7)	3(16.7)	184(10.4)
Manual labour	50(14.0)	40(7.7)	1(0.3)	58(13.0)	2(11.1)	0(0.0)	1(5.6)	152(8.6)
Formal employment	38(10.7)	64(12.4)	0(0.0)	39(8.7)	2(11.1)	8(9.1)	1(5.6)	152(8.6)
Not applicable[a]	4(1.1)	63(12.2)	312(98.1)	3(0.7)	0(0.0)	11(12.5)	2(11.1)	395(22.4)
Missing information	23(6.5)	23(4.5)	0(0.0)	33(7.4)	0(0.0)	3(3.4)	0(0.0)	82(4.7)
Median length of stay+	6(2–12)	11(4–29)	3(1–6)	3(1–7)	–	17(2–108)	1(1–1)	4(2–12)
All	356(100.0)	517(100.0)	318(0.0)	448(100.0)	18(100.0)	88(100.0)	18(100.0)	1763(100.0)

[a]Mostly under 15 years+presented as median number of days (25th–75th percentile)

The proportion categorized as unemployed/low income earners was 65 % but when the under 15 year olds and whose information is missing are excluded, this becomes 70 %. The median number of days patients had stayed in the hospital was 6.

Surgical Wards

The surgical wards were dominated by males (61 %) and like the medical wards people aged 25–55 years were the dominant majority with only a fifth of the inpatients being aged 55 years and above. Unlike the medical wards, the highest proportion of the inpatients on the surgical wards were from other upcountry districts (36 %). Two fifth of the inpatients were married and 35 % had attained at least primary education. Over 59 % were unemployed or had low income employment and this proportion becomes 71 % after removing the under 15 year olds and those whose information was not given. Inpatients on the surgical wards stayed for a median of 11 days in the hospital.

Paediatrics Wards

The paediatric ward was dominated by male children (56.3 %) mostly aged under 5 years (80 %). They were mainly from Wakiso and Kampala (78 %). The ward had the least proportion of inpatients referred from upcountry (11 %). Occupation, marital status and education are not applicable to the in-patients. Inpatients on the ward had on stayed for a median of 3 days.

Obstetrics and Gynecology Wards

A high percentage of these (76 %) were aged 15–34 years and were mainly from Wakiso and Kampala (76 %). They were mainly married (62 %) with a sizable proportion having attained at least secondary education (48 %). Notably, the ward had the second highest proportion of inpatients unemployed (47 %) and (71 %) can be classified as unemployed/low income earners. The median number of days inpatients had stayed at the hospital was 3.

Psychiatry Ward

There were few psychiatry in-patients (18) and a higher proportion were women. They were inpatients from different age groups which were almost equally distributed. Of the adult psychiatric inpatients, over 39 % were from Kampala with referrals from districts neighboring Kampala and Wakiso district being 17 % and those from upcountry districts being 23 %. More than a half (56 %) were single and 67 %

had attained at least secondary school education and 60 % were unemployed. Data on length of stay were not available for the inpatients on the ward. There were no special psycho-geriatric beds but six children's beds.

Cancer Institute

The cancer institute was dominated by women (57 %) and people aged over 34 years (59 %) and they were mainly referrals from districts outside Kampala and the upcountry districts (76 %). Twenty eight percent had attained secondary level education. Thirty six percent were married while more than a fifth (22 %) were widowed or divorced. Thirty nine percent had attained primary level education while 28 % had attained secondary level. Thirty nine percent did not have a job while 67 % can be classified as belonging to the unemployed/low income group. The median number of days inpatients had stayed on the ward was 17.

Heart Institute

In the Heart Institute there were few (18) in-patients who were mainly females (61 %) and aged 45+ (61 %). A half of these had been referred from other districts beyond Kampala and surrounding districts. They were mainly married (44 %) or single (22 %). Thirty nine percent had attained secondary level education and the same proportion was unemployed. Fifty percent can be classified as unemployed/low income earners. Only five patients had information on length of stay and the median was 1 day.

Discussion

The results from this short study have shown that most inpatients in Mulago national referral hospital are female (60 %), youth (15–34) [40 %] or very young (<5) [18 %], from Kampala city (44 %) or Wakiso district (20 %), married (39 %) or single (19 %), had attained at least primary level of education (53 %), and were unemployed/low income earner (54 %). However, there were variations in profiles of inpatients by kind of ward. Of the 1,763 patients, 29 % were admitted on the surgical ward, 25.4 % to the obstetrics and Gynecology ward, 20.2 % to the medical ward, 18 % to the pediatric ward, 5 % to the cancer institute, 1 % to both the psychiatric and heart institute. Among males the commonest causes were surgical (44 %) and pediatrics (25 %) while among females they were obstetrics and gynecology related conditions (29 %) and those that need surgical services (19 %). Very few (eight) inpatients were from outside the country.

The results above have some similarity with those found in Bangladesh. A study by Begum et al. found that 53 % of those in lowest income quintile accounted for

53 % of use of public health services [10]. The users were also more likely to be uneducated. Also the distribution of the inpatients by ward is similar to that found in Muhimbili National referral hospital in Tanzania where they also found that inpatients mostly sought surgical services (37 %) followed by obstetrics and gynaecology services (30 %) and (19 %) paediatric services [5]. It is highly likely these referral cases came from areas where there was a deficit in provision of surgical and medical services and so they sought out for these services at the referral facilities.

The fact that the commonest cause of admission among men were conditions that needed surgery could imply that male medical conditions were appropriately managed at the lower level facilities while among women it was obstetrics and gynaecology conditions, indicating a challenge in provision of obstetric and gynecological conditions at those lower facilities. This is more so in Kampala and Wakiso districts as the majority (76 %) of inpatients on the Obstetrics and Gynecology wards were from these districts.

Most of the inpatients originated from Kampala city and Wakiso district (which surrounds Kampala). This could reflect a deficiency of primary health care facilities in these districts, and so patients were forced to visit a referral hospital despite the fact that they could have been handled at lower level facilities. It could also mean that Mulago is the nearest health facility to them and so it was easier for them to visit Mulago other than other facilities.

The high proportion of the unemployed/low income earners among the inpatients could indicate that the utilization of this facility is mainly by lower level socioeconomic status who may not afford to seek for the expensive private health facility services. It also suggests the government should continue offering free services at the facility since the majority of the patients were low income earners and of low education status.

The surgical ward had the highest proportion of the inpatients from other districts (36 %). This may imply that there is still a limitation in the management of surgical cases in these districts and thus requiring scaling up of surgical services in upcountry facilities. The fact that the paediatric ward had the least proportion of inpatients referred from upcountry could indicate adequate capacity to handle pediatric cases upcountry.

Although the Cancer and the Heart institutes had the least number of in patients (5 % and <1 %, respectively), most of these were patients from districts outside Kampala. This goes to show the challenge of managing cancer and heart condition at peripheral health facilities. In most cases the difficulties is compounded by inadequate diagnostic equipment and a lack of highly specialized personnel at the peripheral health facilities to manage these conditions, hence the need to seek for services at Mulago hospital. Psychiatric cases were also few indicating poor utilization of psychiatric services at general hospitals as is common elsewhere in Africa. The absence of geriatric services at Mulago hospital was a glaring omission which could explain old age degenerative disorders are poorly reflected in the hospitals statistics.

Conclusion

Most of the inpatients had low level of education (primary) regardless of sex, with high levels of unemployment.

The under 5 s and women in the age bracket of 25–55 constituted the biggest majority of the in-patients. Those aged 60 years and above were 10 % of the in-patients.

Most inpatients originate from Kampala and Wakiso districts and most were on the surgical wards, obstetrics and gynecology wards, medical wards and the pediatric wards. The commonest conditions responsible for causing admission were surgical amongst men and obstetric and gynaecological amongst the women.

There was a conspicuous absence of geriatric services despite 10 % of the inpatients being above 60 years old.

Recommendations

The results add more support for the current efforts to decongest the national referral hospital. More resources should be sought to build other hospitals in the city, Wakiso district and surrounding districts to decongest the National referral hospitals. The new facilities should focus more on obstetrics and gynecology, surgical and paediatrics services. There is also a need for a geriatric medicine department.

The standard of Mulago National referral hospital needs to be raised so that it appeals for all categories of the population of the country including the middle and high income groups. That way, it will attract more resources from within and outside the country.

This study could have been more easily carried out using hospital records if they were computerized. We recommend that the government looks for funding to computerize all medical records of the hospital. This will reduce expenditure on monitoring and evaluation of the services in the hospital.

References

1. Sico J. Serving international neurology from Uganda. Neurol Today. 2010;10(8):4.
2. GOU. Report of the committee on health on the ministerial policy statement and the budget estimates for the health sector for the FY 2013/2014. Kampala: Government of Uganda; 2013.
3. MOH. Health sector strategic plan III- 2010/11-2014/15. Kampala: Ministry of Health, Government of Uganda; 2010.
4. MOH. Annual health sector performance report 2012/13. Kampala: Ministry of Health; 2013.
5. Simba, DO, NAA Mbembati, et al. (2008). "Referral pattern of patients received at the National Referral Hospital: challenges in low income countries." East African Journal of Public Health 5(1):6–9.

6. Sanders W, Kravitz J, Lewin S, McKee M. Zimbabwe's hospital referral system: does it work? Health Policy Plan. 1998;13:359–70.
7. GoU, UNFPA. The state of Uganda's population report 2013. Kampala: Government of Uganda and UNFPA; 2013.
8. Nyakaana JB, Sengendo H, Lwasa S. Population, urban development and the environment in Uganda: the case of Kampala city and its environs. Kampala: Faculty of Arts, Makerere University; 2007.
9. UBOS. The 2002 Uganda population and housing census-main report. Kampala; 2005.
10. Begum T, Ali QL, Begum SA, Moral AH, Ensor T, Sen PD, Priti. Who benefits from public health expenditure? Dhaka: Health Economics Unit, Policy and research unit, Ministry of health and welfare, Government of Bangladesh; 2001.

Part II
Selected Causes of Brain Degeneration in Uganda

Chapter 4
HIV-Associated Cognitive Impairment in Sub-Saharan Africa

Noeline Nakasujja

Abstract The HIV/AIDS epidemic is now in its fourth decade in Sub-Saharan Africa where survival of HIV infected individuals has resulted in an increased burden of cognitive impairment among People Living With HIV/AIDS. The greatest risk for the impairment has been among those who are older and of female gender. Various categories of cognitive impairment are now more recognised as affecting the HIV population. The classification for the impairment currently follows the Frascati criteria that subgroups the HIV-Associated Neurocognitive Disorders (HAND) into: HIV Associated Asymptomatic Neurocognitive Impairment (ANI), HIV-1 Associated Mild Neurocognitive Disorder (MND) and HIV 1 Associated Dementia (HAD).

Using cross cultural neuropsychological tools, it has been possible to have screening instruments for detection of possible cases of HIV-associated cognitive impairment that are then further evaluated for confirmation specific impairment.

Among untreated patients with HIV dementia there is a close association with the inflammatory response and cerebral spinal fluid viral load. With the exception of combination antiretroviral therapy, no adjuvant treatments including drugs like minocycline have proven to be effective in reversing HIV-associated neurocognitive impairment.

As long as there is continued limitation on the availability of ART in sub-Saharan Africa, HAND will continue to cause significant HIV-related neurocognitive problems in SSA where the highest HIV infection burden occurs.

Keywords Cognitive impairment • HIV • Africa

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S. Musisi, S. Jacobson (eds.), *Brain Degeneration and Dementia in Sub-Saharan Africa*, DOI 10.1007/978-1-4939-2456-1_4

Introduction

The HIV/AIDS epidemic is now in its fourth decade in Sub-Saharan Africa (SSA). With the increasing availability of combination Antiretroviral Treatment (cART), there has been an observed increase in the survival of HIV infected individuals and this has increased the burden of cognitive impairment among People Living With HIV/AIDS (PLWHIV). Whereas previously only severer forms of cognitive impairment would be detected, categories of mild to moderate impairment are now more recognised as affecting the HIV population [1]. About half of all treated patients with HIV have cognitive impairment, which represents little improvement compared with the pre-cART era. The pattern of cognitive dysfunction is becoming similar to that observed in other chronic degenerative diseases like Alzheimer's [1]. Even with the increased abundance of cART which was initially thought to be the solution to cognitive impairment associated with HIV, the prevalence of the overall figures is still staggering [2, 3]. Multiple challenges arise in SSA where individuals are still limited on the type of antiretroviral regimen they can have access to. It is often suggested that only some cART regime would be the best in penetrating through the blood brain barrier. However the affected individuals are usually poor and depend on what national programs provide in the health systems. Though there is an improvement in survival, individuals suffer the complications that arise with the continued effects of the virus on the brain with an inability of circulating cART to have an effect on the virus within the brain [4]. Nevertheless, the severe forms of neurocognitive impairment that are severely debilitating which often led to death within a year are less [1, 5]. Among patients with severe forms of cognitive impairment, Sacktor et al., have shown that there can be a reversal in the degree of impairment with cART [2, 6]. With the exception of cART, no adjuvant treatments including drugs like minocycline have proven to be effective in reversing HIV-associated neurocognitive impairment [7]. In addition, studies have shown that there is viral escape, where the virus compartmentalizes in cerebral spinal fluid (CSF) escaping the effects of circulating ART thus making the sufferer to continue with cognitive decline [4, 8].

Assessment for HIV-Associated Cognitive Impairment

The classification for cognitive impairment in HIV/AIDS has changed due to refinements in criteria that assess the levels of impairment. Previously the term AIDS dementia complex [5] was used to refer to any HIV-related cognitive impairment. Later, two categories were designated by the American academy of neurology namely; Minor Cognitive Motor Disorder (MCMD) and HIV Associated Dementia (HAD) [9]. Recent refining the definitions of HIV-associated cognitive impairment using neuropsychological test measures have catered for normative comparisons. These tests are, however, not feasible for routine clinical testing and require

expertise and training even for field studies. Currently the Frascati criteria are used in the determination of the different levels of cognitive function in HIV positive individuals. This neuropsychological assessment surveys the following cognitive abilities: verbal/language; attention/working memory; abstraction/executive; memory (learning; recall); speed of information processing; sensory-perceptual, motor skills [9].

Due to limitations in studies of population prevalence data in Africa, most reported studies are of cases identified in HIV care centres and are thus unlikely to represent the community prevalence of the neurocognitive burden brought on by HIV. The use of cross cultural tools to measure cognitive impairment has, however helped clear this picture. A number of recent studies towards this goal have been conducted in Uganda, South Africa and West Africa and these instruments have proven possible for use by non-psychologists [10–13]. Using such tools, it has been possible to have screening instruments for detection of possible cases of HIV-associated cognitive impairment that are then further evaluated for confirmation of the impairment.

One main screening instrument that has been in use since the early 2000 is the International HIV Dementia Scale, IHDS [14]. This instrument was validated in Uganda on a sample of HIV positive individuals and has since been used in a number of other researches on the continent. However the sensitivity and specificity of the instrument are only at 88 % and 55 % [14]. In another validity study by Joska et al. [15], conflicting results showed the IHDS instrument to have a sensitivity and specificity of 45 % and 79 % respectively [15]. The authors then, recommended the inclusion of brief tests for executive function to help improve the IHDS as a screening instrument that would reduce the rate of false negatives. In West Africa similar findings to those in Uganda were found in a study where 85 % of screened individuals tested positive on the IHDS [13]. However the rather high figures indicate the low specificity of the instrument that can be further improved.

Classification for HIV-Associated Neuro-cognitive Disorders, HAND

The term used today to refer to all kinds of neurocognitive impairment associated with HIV infection is HIV-Associated Neurocognitive Disorders or HAND. There are three recognized categories for this classification: HIV Associated Asymptomatic Neurocognitive Impairment (ANI), HIV-1 Associated Mild Neurocognitive Disorder (MND) and HIV-1 Associated Dementia (HAD). The classification has therefore been modified as indicated in the summarized Table 4.1 for the spectrum of cognitive disorders associated with HIV [9].

Concerns on the above classification are pointed towards the category of asymptomatic neurocognitive impairment (ANI) in which only one test is required to fulfil the diagnostic criteria even though two tests are recommended for assessing

Table 4.1 Classification of HIV-associated neurocognitive disorders (HAND)[a]

ANI	**HIV-associated asymptomatic neurocognitive impairment**
	Cognitive impairment involving at least two cognitive domains (performance of at least 1 SD below the mean for norms on neuropsychological tests)
	1. The cognitive impairment does not interfere with everyday functioning
	2. The cognitive impairment does not meet criteria for delirium or dementia
	3. There is no evidence of another pre-existing cause (like depression or substance abuse)
MND	**HIV-1-associated mild neurocognitive disorder**
	Cognitive impairment involving at least two cognitive domains (performance of at least 1 SD below the mean for norms on neuropsychological tests)
	1. The cognitive impairment produces at least mild interference in daily functioning (at least one of the following):
	i. Self-report of reduced mental acuity, inefficiency in work, homemaking, or social functioning
	ii. Observation by knowledgeable others that the individual has undergone at least mild decline in mental acuity with resultant inefficiency in work, homemaking, or social functioning
	2. The cognitive impairment does not meet criteria for delirium or dementia
	3. There is no evidence of another pre-existing cause for the MND
HAD	**HIV-1-associated dementia**
	Marked cognitive impairment involving at least two cognitive domains (performance of at least 2 SD below the mean for norms on neuropsychological tests)
	1. The cognitive impairment produces marked interference with day-to-day functioning in work, home and social activities
	2. The marked cognitive impairment has been present for at least 1 month
	3. The pattern of cognitive impairment does not meet criteria for delirium (e.g., clouding of consciousness is not a prominent feature); or, if delirium is present, criteria for dementia need to have been met on a prior examination when delirium was not present
	4. There is no evidence of another, pre-existing cause for the dementia (e.g., other CNS infection, CNS neoplasm, cerebrovascular disease, pre-existing neurological disease, or severe substance abuse compatible with CNS disorder)

[a]Frascati criteria HAND categories

each cognitive domain. This translates to 20 % of cognitively normal HIV-positive individuals being misclassified as having ANI as a result of many confounding factors; a major one being the definition of functional impairment. Gisslén et al. [16], have cautioned on the applicability of this classification and argued its modification as being warranted. For patients with HAD there is marked acquired impairment in cognitive functioning, involving at least two ability domains. Typically the impairment is in multiple domains, especially in learning of new information, slowed information processing, and defective attention/concentration [10, 17]. Table 4.1 summarizes the criteria for HAND classification.

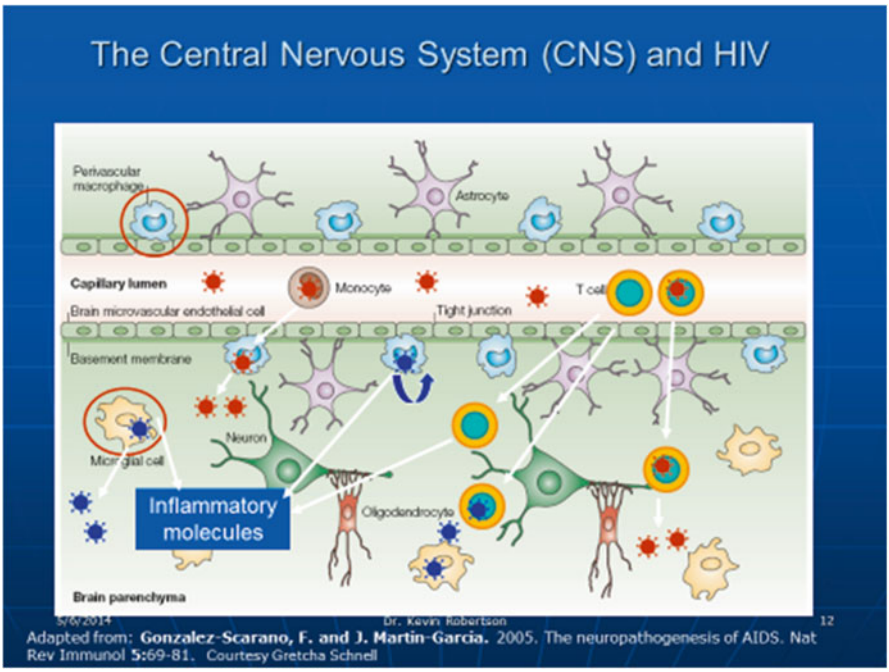

Fig. 4.1 HIV infection of CNS cells

Pathogenesis of HIV-Associated Neurocognitive Disorders, HAND

The direct effect of the HIV virus on the body is on the cellular immune system through depletion of infected CD4 lymphocytes [18]. The effects on the neurological system are through a similar mechanism of attack of brain macrophages and the production of neurotoxins which subsequently damage the brain neurons. Among untreated patients with HIV dementia, there is a close association with the inflammatory response and CSF viral load [19]. Figure 4.1 summarizes the pathogenesis for HAND [20].

HIV-Associated Cognitive Impairment: Evidence from Studies in Uganda

The prevalence of neurocognitive impairment associated with HIV has been considerably researched in Uganda. The initial prevalence among ART naïve individuals found at 31 % has increased to 41 % in more recent years in the population with

higher CD4 counts [3, 14]. The greatest risk for the impairment has been older age and female gender [2, 11]. When tested over time, the initiation of cART contributed significantly to improvement in neurocognitive function in the short term though when followed up over a longer period of time there seems to be no difference among individuals who are on cART versus those who are not especially if they had moderate immunosuppression [2, 6]. Significantly noted in longitudinal studies among HIV positive individuals with cognitive impairment are the persistent high scores for depression symptoms even after an improvement in the neuropsychological functions tests of research participants. This underscores the importance of HIV effects on the brain and the need to have such conditions appropriately screened and treated once identified [21].

There are mainly two common subtypes of HIV clades in Uganda i.e. clade A and clade D. Among patients with advanced immunosuppression, clade D subtype showed an association for neurocognitive impairment [22]. However, there was no difference in the frequency of HIV dementia by clade subtype among those with moderate immunosuppression [3] and no association with compartmentalization between the cerebrospinal fluid and peripheral blood [3].

The double jeopardy of having HIV and psychosis or other opportunistic infections have been confirmed by Nakasujja et al. [7] who found that HIV positive individuals were almost three times more likely to be cognitively impaired on the Mini Mental State Examination (MMSE) as well as on the following cognitive tests: WHO-UCLA Auditory Verbal Learning Test, Verbal Fluency, Color Trails 1 and Color Trails 2. Even when the psychosis cleared the impairment remained higher for the HIV positive group [23]. Similarly, patients that had opportunistic infections like cryptococcal meningitis and had significant short-term neurocognitive impairment improved markedly on treatment with cART over the first 12 months [24].

Conclusion

For the majority of HIV positive patients there is impairment in neurocognitive function. However, severe dementia rarely develops in patients on effective combination antiretroviral therapy, cART. Most patients with mild neurocognitive impairment are clinically stable. The most likely HIV clade to be associated with HAD is clade D and this is the most common clade in Uganda. Typical HIV disease biomarkers (viral load or CD4) are not reliable predictors of HIV-associated cognitive impairment, though inflammatory markers are associated with the impairment. Neuroimaging and cerebrospinal fluid studies could provide new mechanisms to improve our understanding of HIV-Associated Neurocognitive Disorders, HAND. In the presence of depressive illness in cognitively impaired individuals, treating the depression is important, however, even with optimum HIV therapy it is not sufficient to avert cognitive impairment 100 %.

In conclusion, therefore, for as long as there is continued limitation on the availability of ART in sub-Saharan Africa, HAND will continue to cause significant

HIV-related neuropsychiatric problems in SSA where the highest HIV infection burden occurs. Even with the few that get cART milder forms of cognitive impairment persist and alternatives in managing such impairments as memory complaints should be instituted in clinical care.

References

1. Clifford B, Ances B. HIV-associated neurocognitive disorder. Lancet Infect Dis. 2013;13:976–86.
2. Sacktor N, Nakasujja N, Skolasky R, Robertson K, Wong M, Musisi S, Katabira E, Ronald A. Antiretroviral therapy improves cognitive impairment in HIV+ individuals in sub-Saharan Africa. Neurology. 2006;67(2):311–4.
3. Sacktor N, Nakasujja N, Redd A, Manucci J, Laeyendecker O, Wendel S, Porcella S, Martens C, Bruno D, Skolasky R, Okonkwo O, Robertson K, Musisi S, Katabira E, Quinn THJ. HIV subtype is not associated with dementia among individuals with moderate and advanced immunosuppression in Kampala, Uganda. Metab Brain Dis. 2014;29(2):261–8.
4. Letendre S, Marquie-Beck J, Capparelli E, Best B, Clifford D, Collier A, Gelman B, McArthur J, McCutchan J, Morgello S, Simpson D, Grant I, Ellis R, CHARTER Group. Validation of the CNS penetration-effectiveness rank for quantifying antiretroviral penetration into the central nervous system. Arch Neurol. 2008;65(1):65–70.
5. Navia B, Jordan B, Price R. The AIDS dementia complex: I. Clinical features. Ann Neurol. 1986;19:517–24.
6. Sacktor N, Nakasujja N, Okonkwo O, Skolasky R, Robertson K, Musisi S, Katabira EJNJ. Longitudinal neuropsychological test performance among HIV seropositive individuals in Uganda. J Neurovirol. 2013;19(1):48–56.
7. Nakasujja N, Miyahara S, Evans S, Lee A, Musisi S, Katabira E, Robertson K, Ronald A, Clifford D, Sacktor N. Randomized trial of minocycline in the treatment of HIV-associated cognitive impairment. Neurology. 2013;80:196–202.
8. Lucas M, Karrer U, Lucas A, Klenerman P. Viral escape mechanisms–escapology taught by viruses. Int J Exp Pathol. 2001;82(5):269–86.
9. Antinori A, Arendt G, Becker J, et al. Updated research nosology for HIV-associated neurocognitive disorders. Neurology. 2007;69:1789–99.
10. Robertson KR, Nakasujja N, Musisi S, Wong M, Katabira E, Parsons T, Ronald A, Sacktor N. Pattern of neuropsychological performance among HIV positive patients in Uganda. BMC Neurol 2007;7:8.
11. Wong M, Robertson K, Nakasujja N, Skolasky R, Musisi S, Katabira E, Ronald A, Sacktor N, et al. Frequency of and risk factors for HIV dementia in an HIV clinic in sub-Saharan Africa. Neurology. 2007;68:350–5.
12. Georgette K, Kuate C, Cysique L, Fonsah J, Eta S, Doh R, Njamnshi D, Nchindap E, Franklin D, Ellis R, McCutchan J, Binam F, Mbanya D, Heaton R, Njamnshi A. HIV – associated neurocognitive disorders in sub-Saharan Africa: a pilot study in Cameroon. BMC Neurol. 2010;10:60.
13. Atashili J, Gaynes B, Pence B, Tayong G, Kats D, O'donnell J, Ndumbe P, Njamnshi A. Prevalence, characteristics and correlates of a positive-dementia screen in patients on antiretroviral therapy in Bamenda, Cameroon: a cross-sectional study. BMC Neurol. 2013;13:86.
14. Sacktor N, Wong M, Nakasujja N, Skolasky R, Selnes O, Musisi S, Ronald A, Katabira E, Robertson K. The international HIV dementia scale: a new rapid screening test for HIV dementia. AIDS. 2005;19(13):1367–74.
15. Joska JA, Westgarth-Taylor J, Hoare J, Thomas KG, Paul R, Myer L, Stein DJ. Validity of the international HIV dementia scale in South Africa. AIDS Patient Care STDS. 2011; 25(2):95–101.

16. Gisslén M, Price R, Nilsson S. The definition of HIV-associated neurocognitive disorders: are we overestimating the real prevalence? BMC Infect Dis. 2011;11:356.
17. Heaton R, Franklin D, Ellis RJ, et al. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. J Neurovirol. 2011;17:3–16.
18. Cooper E, Lacey C. Laboratory indices of prognosis in HIV infection. Biomed Pharmacother. 1988;42(8):539–45.
19. McMcArthur J, Nance-Sproson T, Griffin D. The diagnostic utility of elevation in cerebrospinal fluid β2-microglobulin in HIV-1 dementia. Neurology. 1992;42:1707–12.
20. González-Scarano F, Martín-García J. The neuropathogenesis of AIDS. Review. Nat Rev Immunol. 2005;5(1):69–81.
21. Nakasujja N, Skolasky R, Musisi S, Allebeck P, Robertson K, Ronald A, Katabira E, Clifford B, Sacktor N . Depression symptoms and cognitive function among individuals with advanced HIV-infection in Uganda. BMC Psychiatry. 2010;10:44.
22. Sacktor N, Nakasujja N, Skolasky R, Rezapour M, Robertson K, Laeyendeker O, Musisi S, Katabira E, Quinn T. HIV subtype D is associated with dementia compared with subtype a in immuno-suppressed individuals at risk of cognitive impairment in Kampala, Uganda. Clin Infect Dis. 2009;49(5):780–6.
23. Nakasujja N, Allebeck P, Agren H, Musisi S, Katabira E. Cognitive dysfunction among HIV positive and HIV negative patients with psychosis in Uganda. PLoS One. 2012;7(9):e44415.
24. Carlson R, Rolfes M, Birkenkamp K, Nakasujja N, Rajasingham R, Meya D, Boulware D. Predictors of neurocognitive outcomes on antiretroviral therapy after cryptococcal meningitis: a prospective cohort study. Metab Brain Dis. 2014;29(2):269–79.

Chapter 5
Vitamin Deficiencies and Neuropsychiatric Disorders in Sub-Saharan Africa

Michael Ssonko

Abstract Deficiencies of vitamins are associated with psychiatric illnesses either by being the primary cause or an exacerbating factor. Psychiatric symptoms could also lead to poor nutrition. Vitamin deficiencies may play a role in compromising patient recovery. Vitamins are organic substances essential for several enzymatic functions. There are 13 known vitamins which are either fat soluble (4 vitamins i.e. KEDA) or water soluble (9 vitamins i.e. C, and the B group). For brain function, B-vitamins are essential in the maintenance of myelin, neuro-transmitter production and the methylation cycle. Fat-soluble vitamins are necessary in inflammatory regulation, regeneration of antioxidants and genetic modification. Vitamin deficiencies will, therefore, cause brain degeneration and will be associated with psychiatric symptoms. Few studies of vitamin deficiencies have been carried out in Sub-Saharan Africa. This chapter presents an overview of vitamins and their relation to neuropsychiatric disorders with the focus on Sub-Saharan Africa.

Keywords Vitamin deficiency • Psychiatric symptoms • Neurotransmission • Brain degeneration

Introduction

Deficiencies of vitamins are associated with psychiatric illnesses either by being the primary cause or an exacerbating factor. Psychiatric symptoms could also lead to poor nutrition. Vitamin deficiencies may play a role in compromising patient recovery.

Vitamins are organic substances essential for several enzymatic functions. There are 13 known vitamins which are either fat soluble (4 vitamins i.e. K, E, D, and A) or water soluble (9 vitamins i.e. C and the B group).

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S. Musisi, S. Jacobson (eds.), *Brain Degeneration and Dementia in Sub-Saharan Africa*, DOI 10.1007/978-1-4939-2456-1_5

Regarding brain function, B vitamins are essential in the maintenance of myelin, neuro-transmitter production and methylation cycle. Fat-soluble vitamins are necessary in inflammatory regulation, regeneration of antioxidants and genetic modification. Vitamin deficiencies will, therefore, cause brain degeneration and will be associated with psychiatric symptoms. Few studies of vitamin deficiencies have been carried out in Sub-Saharan Africa. Below is an overview of vitamins and their relation to neuropsychiatric disorders with the focus on Africa.

Vitamin B1 Deficiency

Thiamine (Vitamin B1) is critical for glucose metabolism. It is a cofactor of α-ketoglutarate dehydrogenase and pyruvate dehydrogenase enzymes both within the citric acid cycle and transketolase enzyme in the pentose phosphate pathway. Severe B1 deficiency which may result from chronic alcoholism, diabetes or malnutrition is usually associated with Wernicke's encephalopathy (WE). WE is clinically characterised by confusion, ataxia, and nystagmus. It is an acute neuropsychiatric disorder which arises as a result of inadequate supply of thiamine to the brain. Confusion and disorientation stem from the brain's inability to oxidize glucose for energy because B1 is a crucial cofactor in glycolysis and the citric acid cycle. Deficiency leads to an increase in free oxygen radicals, cytokines, and alteration of the blood–brain barrier permeability [1].

The WE pathology involves micro-haemorrhages, loss of neurons and gliosis in the periaqueductal grey matter and in the mammillary bodies [2]. Inadequate treatment of WE can predispose a patient to permanent brain damage: the Korsakoff psychosis (confabulation, lack of insight, apathy, retrograde and anterograde amnesia). The amnesia of KS is probably due to the interruption of diencephalic-hippocampal circuits involving the thalamic nuclei and the mammillary bodies [3]. It is recommended that routine management of patients with alcohol-related disease should include thiamine even if neurological signs are absent as described in South Africa [4]. Other thiamine deficiency presentations have been described in Africa. Patients with tropical ataxic neuropathy usually on cassava diet showed evidence of improvement when treated with thiamine [5].

Vitamin B2 (Riboflavin) Deficiency

Riboflavin is important for the reproduction of glutathione, a known antioxidant. B2 is needed to create the essential flavoprotein coenzymes for synthesis of L-methylfolate and for proper utilization of B6. The majority of flavin coenzyme systems help regulate cellular metabolism, whereas the rest are specifically involved in carbohydrate or amino acid metabolism.

Low B2 levels are more prevalent in depressed patients, possibly because of B2's role in the synthesis and function of glutathione [6].

Vitamin B3 Deficiency

Vitamin B3, Niacin, is an essential component of coenzymes NAD/NADP. Niacin can be endogenously synthesized from its natural precursor, tryptophan, a process that requires vitamins B2 and B6.

Pellagra, described as a "3D" syndrome that includes diarrhoea, dermatitis, and dementia, results from niacin deficiency. The main aetiological factors of pellagra are: a deficient diet in niacin; chronic alcoholism; malabsorption; drugs like isoniazid, pyrazinamide, ehtionamide, 6-mercaptopurine, phenobarbital and chloramphenicol. Neuropsychologic manifestations of niacin deficiency include asthenia, depression, hallucinations, confusion, memory loss and psychosis [7].

Vitamin B6 Deficiency

Vitamin B6 (Pyridoxine) is crucial to glycolysis, the methylation cycle, and revitalising glutathione, which is an antioxidant in the brain. Pyridoxine is a coenzyme for the synthesis of neurotransmitters i.e. serotonin, dopamine and GABA. Lower levels of pyridoxal 5- phosphate (active form) as a result of low dietary and plasma B6 are significantly correlated with higher levels of depression with increased risk and severity of depression in geriatric patients [8, 9].

Vitamin B6 deficiency is common (24–56 %) among patients receiving haemodialysis [10]. Women who take oral contraceptives are at increased risk of vitamin B6 deficiency [11].

Vitamin B9 (Folate)

Folate is required in synthesis of neurotransmitters found in the brain and in phospholipid production. Dietary folate must be converted to L-methylfolate for use in the brain. Folate deficiency and insufficiency are common among patients with mood disorders and correlate with illness severity [12].

A meta-analysis of 11 studies of 15,315 persons found those who had low folate levels had a significant risk of depression [13]. In Tunisia, bipolar I patients with hyperhomocysteinemia were found to have reduced levels of folate [14].

Methylenetetrahydrofolate reductase polymorphism was associated with major depression and bipolar disorder [15]. Clinical trials have shown that several forms of folate can enhance antidepressant treatment [16].

Vitamin B12 Deficiency

An essential cofactor, B12 (cobalamin) is needed to produce monoamine neurotransmitters and maintain myelin. Psychiatric manifestations have been described to occur in the presence of low serum B_{12} levels but in the absence of the other well-recognized neurologic and haematologic abnormalities of vitamin B_{12} deficiency [17]. The psychiatric illnesses caused by vitamin B12 deficiency are depression, irritability, agitation, psychosis, and obsessive symptoms [18, 19]. Low B12 levels and elevated homocysteine increase the risk of cognitive decline and Alzheimer's disease and are linked to a 5-fold increase in the rate of brain atrophy [20].

Low levels of serum cobalamin were found among 23 % of the 34 patients in Tunisia with unexplained neurological symptoms without the presence of anaemia. Among the 82 individuals with isolated psychiatric disorders, 14 % of had low serum B12 levels [21]. Ranges of both Serum levels of folic and vitamin B12 levels in a young adult Ugandan population were found to be similar to those in the western countries [22].

The prevalence of low serum vitamin B12 levels among psychiatric patients admitted in Butabika mental hospital using Cobas E411 analyser for serum B12 assay was 28.6 %. The deficiency was 16.4 % [23]. Significant covariates independently associated with low serum vitamin B12 levels included having a DSM-IV diagnosis of Schizophrenia, duration of psychiatric illness $\geq$3 years and duration of hospitalization <3 weeks. The female population was significantly associated with protection from the low serum levels [23]. Irritable mood was a significant finding among HIV infected ART naïve adults in urban Uganda with suboptimal vitamin B12 [24].

Ascorbic Acid or Vitamin C Deficiency

Vitamin C has important biological functions that include carnitine and neurotransmitter biosynthesis, anti-oxidant protection and regeneration of folic acid and vitamin E respectively [25]. Vitamin C's primary role in the brain is as an antioxidant. Oxidative neuronal damage in the free radical theory was supported by plasma vitamin C levels being lower in older persons (aged 65 years and above) with dementia compared to controls [26].

Depression has been found to be a classic psychiatric symptom of vitamin C deficiency.

Ascorbic acid is a cofactor for dopamine beta-hydroxylase enzyme involved in the conversion of dopamine (DA) to norepinephrine. Vitamin C is also a cofactor for the tryptophan-5-hydroxylase enzyme which is required in the conversion of trypto-

phan to 5-hydroxytryptophan (5-HT). Dopamine, noradrenaline, and 5-HT, have important roles in the regulation of mood [27].

Vitamin C intake is significantly lower in older adults (age ≥60) with depression [28]. Some research has shown that patients with schizophrenia have decreased vitamin C levels and dysfunction of antioxidant defences [29].

Vitamin D Deficiency

Vitamin D is produced from cholesterol in the epidermis through exposure to sunlight. Calcitriol the active form of vitamin D is derived from dermal synthesis or ingestion of vitamin D. Increasing evidence reveals vitamin D's role in brain function and development [30]. The pathophysiology of depression is linked to glial and neuronal cells which possess vitamin D receptors [31].

Autism spectrum disorders (ASD) which suggest vitamin D deficiency is not well elaborated in Africa compared to the western industrialized countries with high technological development [32]. The prevalence of ASD among children with developmental disorders in Egypt and Tunisia was documented as 33.6 % and 11.5 % respectively [33]. Among the co-morbid disorders diagnosed in association with ASD among African children, intellectual disability was more common. Belhadj et al. documented co-morbid intellectual disability in over 60 % of cases that were studied [34].

Vitamin E Deficiency

There are 8 isoforms of vitamin E – 4 tocopherols and 4 tocotrienols – that function as fat-soluble antioxidants and also promote innate antioxidant enzymes. Neuronal membranes are protected from oxidation by vitamin E hence reducing inflammation of the brain. Tocotrienols are understood to mediate disease by modifying transcription factors in the brain, for instance glutathione reductase, and superoxide dismutase [35]. Depression has been associated with low plasma vitamin E levels, although other factors excluding dietary intake have been considered [36].

Ataxia with vitamin E deficiency (AVED) is a rare autosomal recessive neurodegenerative disease that occurs in North Africa [37]. Its early identification is essential in order to initiate therapeutic and prophylactic vitamin E supplementation before irreversible damage develops. In Uganda, 63 (30.3 %) of the 208 cases studied showed vitamin E deficiency. Among these, four of five patients with cerebrovascular accidents had vitamin E deficiency [38].

Conclusion

There is minimal or no publications in Africa concerning vitamin deficiencies of vitamins B_2, B_3, B_6, and C. Nonetheless the effect of vitamins on neuropsychiatric disorders is not well studied in Sub Saharan Africa. These deficiencies may ultimately lead to brain degeneration if not corrected as may be seen in none response to psychiatric treatment.

References

1. Page GL, Laight D, Cummings MH. Thiamine deficiency in diabetes mellitus and the impact of thiamine replacement on glucose metabolism and vascular disease. Int J Clin Pract. 2011;65(6):684–90.
2. Victor M, Adams RD, Collins GH. The Wernicke-Korsakoff syndrome. Philadelphia: F.A. Davis; 1971.
3. Thomson AD, Marshall EJ. The natural history of Wernicke's encephalopathy and Korsakoff's psychosis. Alcohol Alcohol. 2006;41:151–8.
4. Naidoo DP, Bramdev A, Cooper K. Wernicke's encephalopathy and alcohol-related disease. Postgrad Med J. 1991;67:978–81.
5. Adamolekun B, Adamolekun WE, Sonibare AD, Sofowora G. A double-blind, placebo-controlled study of the efficacy of thiamine hydrochloride in a seasonal ataxia in Nigerians. Neurology. 1994;44(3 Pt 1):549–51.
6. Naghashpour M, Amani R, Nutr R, et al. Riboflavin status and its association with serum hs-CRP levels among clinical nurses with depression. J Am Coll Nutr. 2011;30(5):340–7.
7. Pitche PT. Pellagre et érythèmes pellagroïdes, Sante 2005;15(3):205–8.
8. Hvas AM, Juul S, Bech P, Nexo E. Vitamin B6 level is associated with symptoms of depression. Psychother Psychosom. 2004;73(6):340–3.
9. Merete C, Falcon LM, Tucker KL. Vitamin B6 is associated with depressive symptomatology in Massachusetts elders. J Am Coll Nutr. 2008;27(3):421–7.
10. Corken M, Porter J. Is vitamin B(6) deficiency an under recognized risk in patients receiving haemodialysis? A systematic review: 2000–2010. Nephrology (Carlton). 2011;16(7):619–25.
11. Wilson SM, Bivins BN, Russell KA, et al. Oral contraceptive use: impact on folate, vitamin B6, and vitamin B12 status. Nutr Rev. 2011;69(10):572–83.
12. Coppen A, Bolander-Gouaille C. Treatment of depression: time to consider folic acid and vitamin B12. J Psychopharmacol. 2005;19(1):59–65.
13. Gilbody S, Lightfoot T, Sheldon T. Is low folate a risk factor for depression? A meta-analysis and exploration of heterogeneity. J Epidemiol Community Health. 2007;61(7):631–7.
14. Ezzaher A, Mouhamed DH, Mechri A, Omezzine A, Neffati F, Douki W, Bouslama A, Gaha L, Najjar MF. Hyperhomocysteinemia in Tunisian bipolar I patients. Psychiatry Clin Neurosci. 2011;65(7):664–71.
15. Gilbody S, Lewis S, Lightfoot T. Methylenetetrahydrofolate reductase (MTHFR) genetic polymorphisms and psychiatric disorders: a HuGE review. Am J Epidemiol. 2007;165(1):1–13.
16. Di Palma C, Urani R, Agricola R, et al. Is methylfolate effective in relieving major depression in chronic alcoholics? A hypothesis of treatment. Curr Ther Res Clin Exp. 1994;55(5):559–68.
17. Herrmann W, Lorenzl S, Obeid R. Review of the role of hyperhomocysteinemia and B-vitamin deficiency in neurological and psychiatric disorders: current evidence and preliminary recommendations. Fortschr Neurol Psychiatr. 2007;75(9):515–27.

18. Lindenbaum J, Healton EB, Savage DG, et al. Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. N Engl J Med. 1988;318(26): 1720–8.
19. Bar-Shai M, Gott D, Marmor S. Acute psychotic depression as a sole manifestation of vitamin B12 deficiency. Psychosomatics. 2011;52(4):384–6.
20. Vogiatzoglou A, Refsum H, Johnston C, et al. Vitamin B12 status and rate of brain volume loss in community-dwelling elderly. Neurology. 2008;71(11):826–32.
21. Maktouf C, Bchir F, Louzir H, Elloumi M, Ben Abid H, Mdhaffer M, Elleuch N, Meddeb B, Mhiri C, Hassen Z, Makni F, Abid M, Cherif O, Rokbani L, Souissi T, Hafsia A, Dellagi K. Clinical spectrum of cobalamin deficiency in Tunisia. Ann Biol Clin. 2007;65(2):135–42.
22. Galukande M, Jombwe J, Fualal J, Baingana R, Gakwaya A. Reference values for serum levels of folic acid and vitamin B12 in a young adult Ugandan population. Afr Health Sci. 2011;11(2):240–3.
23. Ssonko M, Ddungu H, Musisi S. Low serum vitamin B12 levels among psychiatric patients admitted in Butabika mental hospital. BMC Res Notes. 2014;7:90.
24. Semeere AS, Nakanjako D, Ddungu H, Kambugu A, Manabe YC, Colebunders R. Sub-optimal vitamin B-12 levels among ART-naïve HIV-positive individuals in an urban cohort in Uganda. PLoS One. 2012;7(7):e40072.
25. Hathcock JN (2004) Vitamin and mineral safety, 2nd ed. Council for Responsible Nutrition (CRN).
26. Charlton KE, Rabinowitz TL, Geffen LN, Dhansay MA. Lowered plasma vitamin C, but not vitamin E, concentrations in dementia patients. J Nutr Health Aging. 2004;8(2):99–107.
27. DeSantis J. Scurvy and psychiatric symptoms. Perspect Psychiatr Care. 1993;29(1):18–22.
28. Payne ME, Steck SE, George RR, et al. Fruit, vegetable, and antioxidant intakes are lower in older adults with depression. J Acad Nutr Diet. 2012;112(12):2022–7.
29. Dadheech G, Mishra S, Gautam S, et al. Oxidative stress, α-tocopherol, ascorbic acid and reduced glutathione status in schizophrenics. Indian J Clin Biochem. 2006;21(2):34–8.
30. Berk M, Sanders KM, Pasco JA, et al. Vitamin D deficiency may play a role in depression. Med Hypotheses. 2007;69(6):1316–9.
31. Eyles DW, Smith S, Kinobe R, et al. Distribution of the vitamin D receptor and 1 alpha-hydroxylase in human brain. J Chem Neuroanat. 2005;29(1):21–30.
32. Bakare MO, Munir KM. Autism spectrum disorders (ASD) in Africa: a perspective. Afr J Psychiatry. 2011;14:208–10.
33. Seif Eldin A, Habib D, Noufal A, Farrag S, Bazaid K, Al-Sharbati M, et al. Use of M-CHAT for a multinational screening of young children with autism in the Arab countries. Int Rev Psychiatry. 2008;20(3):281–9.
34. Belhadj A, Mrad R, Halayem MB. A clinic and paraclinic study of Tunisian population of children with autism. About 63 cases. Tunis Med. 2006;84(12):763–7.
35. Sen CK, Khanna S, Roy S. Tocotrienol: the natural vitamin E to defend the nervous system? Ann N Y Acad Sci. 2004;1031:127–42.
36. Owen AJ, Batterham MJ, Probst YC, et al. Low plasma vitamin E levels in major depression: diet or disease? Eur J Clin Nutr. 2005;59(2):304–6.
37. Cavalier L, Ouahchi K, Kayden HJ, Di Donato S, Reutenauer L, Mandel JL, Koenig M. Ataxia with isolated vitamin E deficiency: heterogeneity of mutations and phenotypic variability in a large number of families. Am J Hum Genet. 1998;62:301–10.
38. Tulloch JA, Sood NK. Vitamin E deficiency in Uganda. Am J Clin Nutr. 1967;20(8):884–97.

Chapter 6
Environmental Toxins as Causes of Brain Degeneration in Sub-Saharan Africa

Tom H.A.M. Olewe

Abstract Brain degeneration, especially Dementia is a complex human disease. The Alzheimer's Association estimates that one in 10 persons over 65 and nearly half of those over 85 have Alzheimer's disease. There is paucity of data on the prevalence of dementia in Sub-Saharan Africa. Available data suggests a general prevalence of dementia at 6.4 % in Tanzania and HIV related dementia at 31 % in Uganda. Despite the growing burden of dementia in low-income countries, there are few previous data on the prevalence, causes and risk factors of dementia in sub-Saharan Africa.

Therefore, it is important to identify protective and risk factors for dementia to prevent this disease at an early stage. Several factors are related to dementia, e.g. age, ethnicity, sex, genetic factors, physical activity, smoking, drug use, education level, alcohol consumption, body mass index, co-morbidity, and environmental factors. Due to paucity of Sub-Saharan African data, this review looks at studies done elsewhere to evaluate the association between environmental toxins and risk of dementia, especially Alzheimer's and Parkinson's diseases. We have examined whether evidence from previous studies on association between toxin environmental exposures and dementia is of sufficient strength to warrant specific recommendations for behavioral, lifestyle, or pharmaceutical interventions/modifications targeted to these endpoints. We also suggest future research directions for researchers in dementia-related fields in Sub-Saharan Africa.

Keywords Dementia • Alzheimer's disease • Environmental toxins • Sub-Saharan Africa

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S. Musisi, S. Jacobson (eds.), *Brain Degeneration and Dementia in Sub-Saharan Africa*, DOI 10.1007/978-1-4939-2456-1_6

What Is Dementia?

Dementia is an acquired complex of intellectual deterioration which affects at least two areas of cognitive function. Decline must affect ability to function normally. It is a syndrome, not a diagnosis. The executive functions which are affected include: making a plan and carrying it out, weighing information and making good decisions, initiating activities, appropriate social behavior as well as changes in personality. Personality characteristics and denial of memory problems are also associated with executive dysfunction. In addition, the cognitive impairments must be severe enough to cause impairment in social and occupational functioning. Importantly, the decline must represent a decline from a previously higher level of functioning. The cognitive deficits occurring exclusively during the course of delirium, usually short-term, should not be diagnosed as dementia. The Alzheimer's Association estimates that one in 10 persons over 65 years and nearly half of those over 85 years have Alzheimer's disease (http://health.usnews.com/health-conditions/brain-health/alzheimers-disease, 30/10/12).

Types and Causes of Dementia

Some of the major disorders causing dementia are;

- Degenerative diseases e.g. Alzheimer's disease, Pick's disease etc.;
- Vascular dementia e.g. multi-infarct dementia;
- Anoxic dementia e.g. secondary to cardiac arrest);
- Traumatic dementia e.g. dementia pugilistica [boxer's dementia];
- Infectious dementia e.g. Creutzfeldt-Jakob Disease, HIV-associated dementia etc.
- Toxic dementia e.g. alcoholic dementia.

There are many different types of dementia (Table 6.1). It is however still unknown how some diseases may be linked to dementia.

Risk Factors

Many factors can eventually lead to dementia. Some can't be changed while other can be addressed to reduce the risk.

Table 6.1 Types of dementia

Type of dementia	Percentage of all dementia types (approximate) (%)	Causes
Alzheimer's disease	60	Degenerative disease causing "plaques and tangles" to build up in the brain tissues that kill and shrinks the brain
Lewy body dementia	15	Degenerative disease associated with an accumulation of "Lewy Bodies" in the brain causing impairment in cognitive function
Mixed dementia	10	Combination of degenerative disease and other type of dementia
Vascular dementia (multi-infarct or mini-strokes)	5	Circulatory disease of heart and blood vessels resulting in stroke or mini-stroke that damage areas of the brain
Other dementias	10	
1. Frontal lobe dementia and Picks disease		1. Affects frontal lobe, behavior problems
2. Creutzfeldt-Jakob disease		2. Viral disease
3. Multiple sclerosis, Parkinson's disease, Huntington's chorea		3. Diseases of the nervous system
4. Brain damage alcohol abuse, toxins		4. Brain trauma, damage may improve if toxins are removed

Source: Modified from "Definition of Dementia," (Compiled by Wisconsin Bureau of Aging & Long Term Care Resources, Department of Health and Family Services 4/2403 rev. http://www.dhs.wisconsin.gov/aging/dementia.htm, downloaded on 30/10/12)

Non-modifiable Risk Factors

- **Age.** The risk of Alzheimer's disease, vascular dementia and several other dementias increases significantly with age [1]. However, dementia isn't a normal part of aging.
- **Family history.** People with a family history of dementia are at greater risk of developing it. However, many people with a family history never develop symptoms, and many people without a family history do. If they have specific genetic mutations, they are at significantly greater risk of developing certain types of dementia [2].
- **Down syndrome.** By the time they reach middle age, most people with Down syndrome develop the plaques and tangles characteristic of Alzheimer's disease, according to studies [3]. Many, but not all, also develop dementia.

Modifiable Risk Factors

The following factors can be controlled to reduce the risk of dementia:

- **Alcohol use.** Alcohol consumption is one possible risk factor for Alzheimer's Dementia, AD. Alcoholism is associated with extensive cognitive problems [4], including alcoholic dementia [5]. The effects of alcohol on cognition, brain disorders, and brain chemistry are somewhat similar to AD's effects on these three areas, it possible that alcohol use might increase the risk of developing AD [6].
- **Atherosclerosis.** This buildup of plaques is a significant risk factor for vascular dementia as it may lead to stroke. Studies have also shown a possible link between atherosclerosis and Alzheimer's disease [7]
- **Blood pressure.** Uncontrolled hypertension is a risk of developing Alzheimer's disease and vascular dementia. Cumulative evidence implicates hypertension in the pathogenesis of AD [8, 9]
- **Cholesterol.** High levels of low-density lipoprotein (LDL) cholesterol can significantly increase the risk of developing vascular dementia [10]. Some research has also linked high cholesterol levels in middle age each increase the risk of going on to develop AD in later life [11].
- **Depression.** Late-life depression, especially in men, may be an early indication for the development of Alzheimer's-related dementia [12].
- **Diabetes.** People with Type 2 diabetes have an increased risk of developing both Alzheimer's disease and vascular dementia [13].
- **High estrogen levels.** High levels of total estrogen in women have been associated with greater risk of developing dementia [14–16].
- **Homocysteine blood levels.** Elevated blood levels of homocysteine – a type of amino acid produced in the body – may increase the risk of developing Alzheimer's disease and vascular dementia [17].
- **Smoking.** It likely increases the risk of developing dementia because it's a risk factor for atherosclerosis and other types of vascular disease. Recent prospective studies on cohorts without dementia suggest that smokers have a significantly increased risk of dementia, including AD [18, 19].

Environmental Toxins and Dementia

Dementia may originate from environmental toxic substances, namely exposure to heavy metals such as lead, mercury and aluminum; as well as to carbon monoxide, solvents, pesticides and electromagnetic fields [20]. This tends to affect exposed individuals at a relatively young age and the optimal preventative strategies include avoidance of the toxic substances.

Toxic encephalopathy is a general term used to describe any sort of cerebral damage that comes from the use of or exposure to toxic compounds, chemicals or

Table 6.2 Effects of environmental toxins on human health

Metal	Organic diseases	Neurologic and psychiatric effects [23]
Aluminum	Joint pain, bone calcium loss aneamia [24]	Dementia, Alzheimers, Parkinsons, Encephalopathy with loss of memory, concentration and mobility
Arsenic	Type 2 diabetes [25]	Damage to the nervous system leading to weakness, deafness, paresthesia, organic psychosis with drowsiness, agitation, stupor, delirium, schizophrenia
Cadmium	Damage to kidney and lungs, fragile bones, aneamia, increased risk of cancer if inhaled [26]	No reference found at this stage
Mercury	Brain damage, Autoimmune diseases e.g. Rheumatoid Arthritis [27], Cardiovascular diseases [28], liver cancer	Diminished intelligence, speech disorders, restlessness, aggressiveness, visual and hearing disorders, polyneuropathy, myasthenia gravis, Alzheimers
Nickel	Allergies, dermatitis, Eczema [29]	Headache, dizziness, lack of sleep
Lead	Hematological and Cardiovascular effects e.g. hypertension MLEWE [55], kidney damage [30]	Depression that may lead to suicide, lack of attention, damage to visual intelligence and motor function, memory disorder, learning difficulties, fatigue, agitation, aggressivess, psychoses, hallucinations, peripheral polyneuropathy, encephalopathy, saturnism (lead poisoning)
Organic zinc	Stomach cramps, nausea, vomiting, anaemia, damage to the pancreas	Cerebral edema with nausea, vomiting, dizziness, visual disorder, cramps, forgetfulness, fatigue, lack of interest, headaches, sleeping difficulties

Source: Social, Health and Family Affairs Committee, Parliamentary Assembly of the Council of Europe. Health hazards of heavy metals. Doc. 12613, 12 May 2011. http://assembly.coe.int/ASP/Doc/XrefViewPDF.asp?FileID=12818&Language=EN

metals [21]. This damage is sometimes reparable, but in cases in which the damage persists, the risk for development of degenerative dementia increases.

Exposure to any kind of toxic substance with a negative effect on the brain can cause toxic encephalopathy, and ultimately, the onset of dementia. Some of the most common environmental toxic substances that can cause this damage are:

- **Heavy metals:** Mercury, lead, aluminum, arsenic, lead, toluene and lithium, even in small doses, can have a long-term damaging effect on the brain [22] leading to both encephalopathy and dementia (Table 6.2).
- **Pesticides:** Many families of pesticides are known to contain neurotoxic properties [31] that cause serious central nervous system damage e.g., carbamates, organophosphates, organochlorines, and bipyridyles [32]. Evidence consistently suggests that a higher risk of Parkinson's Dementia (PD) is associated with pesticides and that a higher risk of AD is associated with pesticides [33].

- **Solvents:** It is recognized that exposure to solvents can be neurotoxic [34]. However, an association between solvent exposure and neuro-degeneration, particularly AD, has yet to be established. Some studies have demonstrated a moderate-to-strong association between solvent exposure and AD, with a greater effect in men and more years of exposure [35].
- **Electromagnetic fields:** Although no documented causal relationship between occupational electromagnetic field (EMF) exposure and AD has been found, a link between occupations involving exposure to electric and magnetic fields and the subsequent development of AD has been hypothesized. Some research findings [36] suggest that EMF exposure may contribute to an increased production of b-amyloid in the brain, which might eventually result in AD.
- **Carbon Monoxide:** In patients with acute poisoning, 30 % or more may experience delayed onset of neuropsychiatric symptoms [37]. Symptoms include cognitive and personality changes, dementia, psychosis, Parkinsonism, amnesia, depression, and incontinence

Even small amounts of these toxic materials, especially over a long period of time, can cause gradual mental deterioration.

Association Between Toxic Environmental Exposures and Dementia

This section examines whether evidence from previous studies on association between toxin environmental exposures and dementia is of sufficient strength to warrant specific recommendations for behavioral, lifestyle, or pharmaceutical interventions/modifications targeted to these endpoints.

Williams et al. [38] identified a systematic review by Santibanez et al. [39], that examined occupational risk factors for Alzheimer's disease (AD), focusing on the associations between AD and pesticides, solvents, electromagnetic fields, lead, and aluminum in the workplace. The review included 21 case-control studies and three cohort studies published between 1984 and 2003. Some studies examined multiple factors, and number of studies and subject counts are included for each exposure. Therefore, the study count in Table 6.3 exceeds the 22 studies identified. Case control studies were included in spite of the inherent weakness for establishing causality, due to paucity of data from cohort studies. Further, exposures to specific toxic substances are relatively uncommon and would require very large sample sizes to have sufficient power to detect an effect in general community samples.

Two cohort studies reported higher adjusted relative risks for AD with exposure to defoliants and fumigants (RR 4.35; 95 % CI 1.05–17.90) and pesticides in men [RR 2.39, 1.02–5.63] [40]. The single cohort study evaluating solvent exposure [41] did not find an association with AD (RR 0.88; 95 % CI 0.31–2.50). Studies of lead exposure were all case-control design and assessed as low quality; none showed a statistically significant association with AD. One study of aluminum exposure was

Table 6.3 Toxic environmental factors and risk of developing AD – characteristics of studies reviewed by Santibanez et al. [39]

Risk factor	Studies[a]	Subjects[a]	Countries
Solvents	10 case control	3,748	North America (6), Western Europe (2), Asia (2), Canada
	1 cohort	694	
Electromagnetic fields	6 case control	6,205	U.S.A (4), Western Europe (2), U.S.A
	1 cohort	20,068	
Pesticides	4 case control	1,471	Canada (2), U.S.A (1), Australia (1), Canada (1), France (1)
	2 cohort	2,201	
Lead	6 case control	2,182	U.S.A (4), U.K (1), Australia (1)
Aluminium	3 case control	1,056	U.S.A (1), U.K (1), Australia (1)

Source: Williams et al. [38] (Evidence Reports/Technology Assessments, No. 193.) Available from: http://www.ncbi.nlm.nih.gov/books/NBK47456

[a]Some studies examined multiple factors, and number of studies and subject counts are included for each exposure. Therefore, the study count in this table exceeds the 22 studies identified

case-control study and found no association with AD [RR 0.95; 95 % CI 0.5–1.9] [42]. Similarly, the two other case-control studies [43, 44] did not find any association between aluminum and AD. Rondeau et al. [45] in cohort study observed that the risk of AD was increased for aluminum intake ≥0.1 mg/day (RR 1.34; 95 % CI 1.09–1.65) and there was no dose response relationship.

Using a subgroup from the Canadian Study of Health and Aging (15 % of the cohort), Kroger et al. [46] used a nested case-control design to evaluate the association between blood mercury levels and AD. After a median of 4.9 years, individuals in the 3rd (OR 0.41; 95 % CI 0.23–0.74) and 4th quartiles of exposure (OR 0.56, 0.32–0.99) were at lower risk for AD. However, the relatively low participation rate may have introduced significant selection bias. Kamel et al. [47] observed that exposure to certain pesticides may increase risk of Parkinson disease (PD), a cause of dementia. Lee et al. [48] also found that traumatic brain injury and paraquat exposure each increased the risk of PD moderately, with exposure to both factors almost tripled PD risk. These environmental factors seem to act together to increase PD risk in a more than additive manner.

Conclusions and Recommendations

In systematic review, few cohort studies examined the association between toxic-environmental exposures and risk of dementia. Most case-control studies had important methodological limitations that may have biased the results. Among the exposures considered, only pesticides showed a consistent association with AD and PD. Hence, there is justification for specific recommendations for behavioral, lifestyle and pharmaceutical interventions/modifications to reduce exposure to pesticides.

Despite the growing burden of dementia in low-income countries, there are few previous data on the prevalence, causes and risk factors of dementia in sub-Saharan Africa. The prevalence of dementia of 6.4 % (95 % CI 4.9–7.9), in this rural Tanzanian population is similar to that reported in high-income countries [49]. In a Ugandan study 31 % of the HIV-positive patients were found have HIV-Associated Dementia and these were frequently patients of advanced disease stage and decreased CD4 count [50–52]. There is need for further research to determine the general prevalence of dementia in Sub-Saharan Africa as well the measure of association between dementia and potential environmental toxins.

References

1. Shaji KS, et al. Caregivers of patients with Alzheimer's disease: a qualitative study from the Indian 10/66 Dementia Research Network. Int J Geriatr Psychiatry. 2002;18:1–6.
2. Saunders AM, et al. Association of apolipoprotein E allele e4 with late-onset familial and sporadic Alzheimer's disease. Neurology. 1993;43:1467–72.
3. Lisa RS, Rikus HC. Down's syndrome and dementia. Adv Psychiatr Treat. 2004;10:50–8.
4. Evert DL, Oscar-Berman M. Alcohol-related cognitive impairments: an overview of how alcoholism may affect the workings of the brain. Alcohol Health Res World. 1995;19(2):89–96.
5. Smith DM, Atkinson RM. Alcoholism and dementia. In: Gurnack AM, editor. Older adults' misuse of alcohol, medicines, and other drugs: research and practice issues. New York: Springer; 1997. p. 132–57.
6. Tyas SL. Are tobacco and alcohol use related to Alzheimer's disease? A critical assessment of the evidence and its implications. Addict Biol. 1996;1:237–54.
7. Casserly I, Topol E. Convergence of atherosclerosis and Alzheimer's disease: inflammation, cholesterol, and misfolded proteins. Lancet. 2004;363:1139–46.
8. Obisesan TO. Hypertension and cognitive function. Clin Geriatr Med. 2009;25(2):259–88. doi:10.1016/j.cger.2009.03.002.
9. Skoog I, et al. 15-year longitudinal study of blood pressure and dementia. Lancet. 1996;347:1141–5.
10. Watanabe T, Koba S, Kawamura M, Itokawa M, Idei T, Nakagawa Y, Iguchi T, Katagiri T. Small dense low-density lipoprotein and carotid atherosclerosis in relation to vascular dementia. Presented in part at the 13th International Symposium on Atherosclerosis, Kyoto, Japan, September 28-October 2, 2003. Metabolism. 2004;53(Apr):476–82.
11. Kivipelto M, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. BMJ. 2001;322:1447–51.
12. Barnes DE, Yaffe K, Byers AL, McCormick M, Schaefer C, Whitmer RA. Midlife vs late-life depressive symptoms and risk of dementia: differential effects for Alzheimer disease and vascular dementia. Arch Gen Psychiatry. 2012;69(5):493–8.
13. Velayudhan L, Poppe M, Archer N, Proitsi P, Brown RG, Lovestone S. Risk of developing dementia in people with diabetes and mild cognitive impairment. Br J Psychiatry. 2010;196:36–40.
14. Rapp SR, Espeland MA, Shumaker SA, WHIMS Investigators, et al. Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA. 2003;289(20):2663–72.
15. Shumaker SA, Legault C, Rapp SR, WHIMS Investigators, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA. 2003;289(20):2651–62.

16. den Heijer T, Geerlings MI, Hofman A, et al. Higher estrogen levels are not associated with larger hippocampi and better memory performance. Arch Neurol. 2003;60(2):213–20.
17. Garcia A, Zanibbi K. Homocysteine and cognitive function in elderly people. Can Med Assoc J. 2004;171(8):897–904.
18. Ott A, Slooter AJ, Hofman A, et al. Smoking and risk of dementia and Alzheimer's disease in a population-based cohort study: the Rotterdam Study. Lancet. 1998;351:1840–3.
19. Merchant C, Tang MX, Albert S, et al. The influence of smoking on the risk of Alzheimer's disease. Neurology. 1999;52:1408–12.
20. Schofield P. Dementia associated with toxic causes and autoimmune disease. Int Psychogeriatr. 2005;17:S129–47. doi:10.1017/S1041610205001997.
21. Dobbs MR. Toxic encephalopathy. Semin Neurol. 2011;31(2):184–93.
22. Ghosh A. Endocrine, metabolic, nutritional, and toxic disorders leading to dementia. Ann Indian Acad Neurol. 2010;13 Suppl 2:S63–8. doi:10.4103/0972-2327.74247.
23. Jennrich P. Schwermetalle – Ursache von Zivilisationskrankheiten und ihre erfolgreiche Behandlung [Heavy metals – a cause of lifestyle diseases and their successful treatment], Fachmagazin, CO'MED, 03/06. Various sources: daily and scientific press.
24. L'aluminium empoisonne notre vie quotidienne. *Le Monde,* 15 September 2010; Virginie Belle, *Quand l'aluminiumnous empoisonne*, Editions Max Milo, 2010.
25. Navas-Acien A, et al. Arsenic exposure and prevalence of type 2 diabetes in US adults. www.jama.com (November 2010).
26. First Nations Environmental Health Innovation Network, Cadmium fact sheet, Canada. www.fnehin.ca (2008).
27. Nyland JF. Mercury linked to immune changes seen in autoimmune disease. Synopsis of a 2010 study by Gardner, Nyland, Silva, Ventura, deSouza and Silbergeld. www.environmental-healthnews.org (April 2010).
28. Boffetta et al. Mortality from cardiovascular diseases and exposure to inorganic mercury. Occup Environ Med. 2001. www.oem.bmj.com
29. Ontario Ministry of the Environment. Fact sheet: nickel in the environment; April 2011.
30. GDS/Sous-direction de la gestion des risques des milieux: Les effets du plomb sur la santé, Paris; 2002.
31. Gauthier E, Fortier I, Courchesne F, et al. Environmental pesticide exposure as a risk factor for Alzheimer's disease: a case-control study. Environ Res. 2001;86:37–45.
32. Blain PG. Aspects of pesticide toxicology. Adverse drug react. Acute Poison Rev. 1990;9:37–68. http://health.usnews.com/health-conditions/brain-health/alzheimers-disease, downloaded on 30 Oct 2012.
33. Campdelacreu J. Parkinson disease and Alzheimer disease: environmental risk factors. Neurologia, 13 Jun 2012. PubMed PMID: 22703631.
34. Arlien-Soborg P, Hansen L, Ladefoged O, et al. Report on a conference on organic solvents and the nervous system. Neurotoxicol Teratol. 1992;14(1):81–2.
35. Kukull WA, Larson EB, Bowen JD, et al. Solvent exposure as a risk factor for Alzheimer's disease: a case-control study. Am J Epidemiol. 1995;141(11):1059–79.
36. Sobel E, Davanipour Z, Sulkava R, et al. Occupation with exposure to electromagnetic fields: a possible risk factor for Alzheimer's disease. Am J Epidemiol. 1995;142(5):515–24.
37. Ernst A, Zibrak JD. Carbon monoxide poisoning. N Engl J Med. 1998;339:1603–8. http://health.usnews.com/health-conditions/brain-health/alzheimers-disease, downloaded on 30 Oct 2012.
38. Williams JW, Plassman BL, Burke J, Holsinger T, Benjamin S. Preventing Alzheimer's disease and cognitive decline. Evidence report/technology assessment no. 193 (Prepared by the Duke Evidence-based Practice Center under Contract No. HHSA 290-2007-10066-I.) AHRQ Publication No. 10-E005. Rockville: Agency for Healthcare Research and Quality; April 2010.
39. Santibanez M, Bolumar F, Garcia AM, et al. Occupational risk factors in Alzheimer's disease: a review assessing the quality of published epidemiological studies. Occup Environ Med. 2007;64(11):723–32.

40. Baldi I, Lebailly P, Mohammed-Brahim B, et al. Neurodegenerative diseases and exposure to pesticides in the elderly. Am J Epidemiol. 2003;157(5):409–14.
41. Tyas SL, Manfreda J, Strain LA, et al. Risk factors for Alzheimer's disease: a population-based, longitudinal study in Manitoba, Canada. Int J Epidemiol. 2001;30(3):590–7.
42. Salib E, Hillier V. A case-control study of Alzheimer's disease and aluminium occupation. Br J Psychiatry. 1996;168(2):244–9.
43. Gun RT, Korten AE, Jorm AF, et al. Occupational risk factors for Alzheimer disease: a case-control study. Alzheimer Dis Assoc Disord. 1997;11(1):21–7.
44. Graves AB, Rosner D, Echeverria D, et al. Occupational exposures to solvents and aluminium and estimated risk of Alzheimer's disease. Occup Environ Med. 1998;55(9):627–33.
45. Rondeau V, Jacqmin-Gadda H, Commenges D, et al. Aluminum and silica in drinking water and the risk of Alzheimer's disease or cognitive decline: findings from 15-year follow-up of the PAQUID cohort. Am J Epidemiol. 2009;169(4):489–96.
46. Kroger E, Verreault R, Carmichael PH, et al. Omega-3 fatty acids and risk of dementia: the Canadian Study of Health and Aging. Am J Clin Nutr. 2009;90(1):184–92.
47. Kamel F, Tanner C, Umbach D, Hoppin J, Alavanja M, Blair A, Comyns K, Goldman S, Korell M, Langston J, Ross G, Sandler D. Pesticide exposure and self-reported Parkinson's disease in the agricultural health study. Am J Epidemiol. 2007;165(4):364–74.
48. Lee PC, Bordelon Y, Bronstein J, Ritz B. Traumatic brain injury, paraquat exposure, and their relationship to Parkinson disease. Neurology. 2012;79(20):2061–6.
49. Longdon AR, Paddick SM, Kisoli A, Dotchin C, Gray WK, Dewhurst F, Chaote P, Teodorczuk A, Dewhurst M, Jusabani AM, Walker R. The prevalence of dementia in rural Tanzania: a cross-sectional community-based study. Int J Geriatr Psychiatry. 2012. doi:10.1002/gps.3880.
50. Sacktor N, Wong M, Nakasujja N, Musisi S, et al. Risk factors For HIV-dementia in sub-Saharan Africa. J Neurovirol. 2004;10:S3–83.
51. Sacktor N, Nakasujja N, Musisi S, Wong M, et al. The international HIV dementia scale: a new rapid screening test for dementia. AIDS. 2005;19:1367–74.
52. Wong MH, Robertson K, Nakasujja N, Skolasky R, Musisi S, Katabira E, McArthur JC, Ronald A, Sacktor N. Frequency of and risk factors for HIV dementia in an HIV clinic in sub-Saharan Africa. Neurology. 2007;68(5):350–5.
54. Espeland MA, Gu L, Masaki KH, et al. Association between reported alcohol intake and cognition: results from the Women's Health Initiative Memory Study. Am J Epidemiol. 2005;161(3):228–38.
55. Blood Lead Levels And Potental Environmental Exposures Among Children Under Five Years In Kibera Slums, Nairobi. Tom M. Olewe; Mwanthi, Mutuku A.; Wang'ombe, Joseph K.; Griffiths, Jeffrey K. // East African Journal Of Public Health;Apr 2009, Vol. 6 Issue 1, P6

Chapter 7
Childhood Threats to Adult Cognition in Sub-Saharan Africa: Malaria, Anemia, Stunting, Enteric Enteropathy, and the Microbiome of Malnutrition

Jeffrey K. Griffiths and Joyce K. Kikafunda

Abstract Many common childhood conditions are associated with cognitive deficits. While some causes of impaired cognition, such as lead exposure, are well understood, other common conditions in countries such as Uganda – malnutrition, anemia and malaria – are not sufficiently recognized. In this chapter we discuss stunting and its root causes of undernutrition, a lack of sanitation and its relationship to environmental enteropathy and the intestinal microbiome. We also review information about iron-deficiency anemia and malaria, and their neurological and cognitive consequences. We believe that cognitive declines later in life, during adulthood, may be prevented or delayed by addressing these childhood threats to cognition.

Keywords Cognition • Dementia • Brain volume • Gut microbiome • Iron-deficiency anemia • Malaria • Stunting • Undernutrition • Enteric enteropathy

Funding Funding was provided by the US Agency for International Development (USAID) Feed the Future Innovation Laboratory: Collaborative Research in Nutrition for Africa (award number AID-OAA-L-10-00006 to Tufts University). The content of this paper is solely the responsibility of the authors and does not necessarily represent the official views of USAID.

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S. Musisi, S. Jacobson (eds.), *Brain Degeneration and Dementia in Sub-Saharan Africa*, DOI 10.1007/978-1-4939-2456-1_7

Abbreviations

ALA	Alpha linoleic acid
ApoE	Apolipoprotein E
DHA	Docosahexaenoic acid
DHS	Demographic and Health Survey
EE	Environmental enteropathy
EPA	Eicosapentaenoic acid
GABA	*gamma*-aminobutyric acid
IDA	Iron deficiency anemia
Pb	Lead
PRBCs	Parasitized red blood cells
TCA	Tricarboxylic acid

Introduction: Looking Forward from Childhood to Adulthood

Dementia in adulthood is marked by a spectrum of behavioral and cognitive changes. These include memory loss, difficulties with planning and solving problems, temporal and spatial confusion, poor judgment and decision making. Following conversations becomes difficult and withdrawal from social activities is common, as are mood and personality changes such as confusion, depression, fearfulness, and anxiety. Progressive declines in cognitive function may lead to the inability to recognize family members or friends, and the need for assistance with dressing, toileting, and other common activities of daily life. As the fluency of social interactions declines, the burden of care increases for family members and spouses, and issues such as financial competency and secondary medical illnesses arise. Understandably, a focus on identifying and preventing causes of cognitive loss or the secondary complications of dementia has arisen. The costs borne by individuals, by families, and by society at large are high, and are predicted to rise as lifespans increase in many countries. In this communication we extend the timeline for prevention backwards from adulthood to infancy and even before birth (Fig. 7.1). We believe major opportunities for improving adult and elderly cognition are found in this approach. Furthermore, we detail specific threats to cognition found in children, contextualized to the situation of sub-Saharan Africa.

It is generally agreed that in adults, the prevention, identification, and treatment of diabetes and the metabolic syndrome may prevent or delay cognitive decline. The interactions between cardiovascular and cerebrovascular disease, Alzheimer's disease, depression, and other conditions such as tobacco use are still being delineated. For example, the presence of the apolipoprotein E (ApoE) ε4 allele (gene), involved in lipoprotein catabolism and modulation of the immune system, is predictive of both the development of Alzheimer's disease, and non-Alzheimer's cognitive decline as well [1]. However, we note that these causative conditions may differ

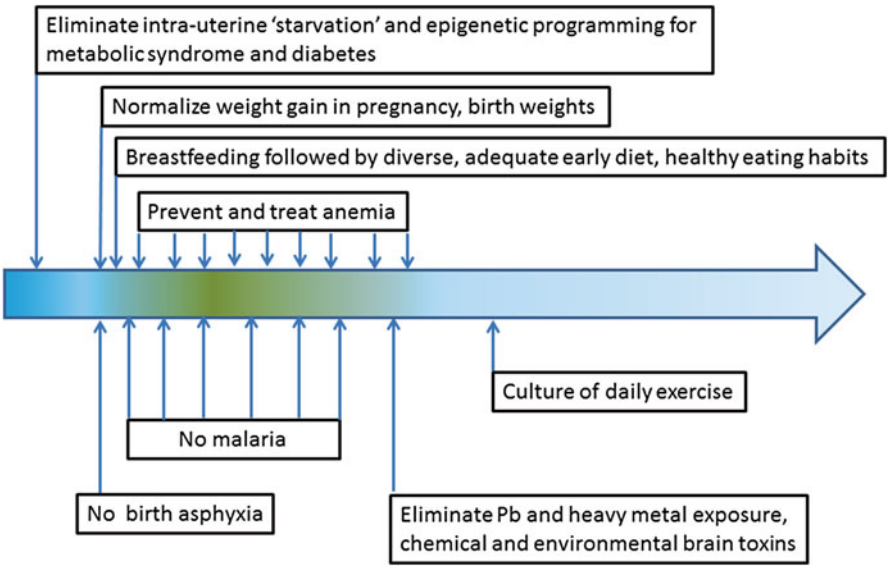

Fig. 7.1 Childhood strategies to improve adult cognition

between the countries where these risk factors have been identified and a low-income sub-Saharan country such as Uganda. For example, most (98–99 %) of the genetic variation in the human race exists in Africa [2, 3]. Other genes besides ApoE are likely important determinants of cognitive decline. Thus, the genetic contributions to diabetes and the metabolic syndrome can be expected to differ between African and non-African populations. Furthermore, traditional African diets are often low in saturated fats and high in fruits and vegetables and are closer to the Mediterranean diets than to the typical 'Western' diet which is high in animal protein and fats, and low in fruits and vegetables. Lastly, there is now good evidence that promoters of cognitive loss – diabetes, obesity, and cardiovascular disease – may evolve somewhat differently in low and middle income countries than in the better studied high income countries [4–6]. All of these argue for additional research into not only causation but also prevention for the African population.

A substantial body of literature has addressed the loss of both grey and white matter brain in the aging brain, as well as changing neuronal morphology with decreasing dendritic arbors and spines. Total brain volume loss, corrected for total intracranial volume, has been shown to be predictive for the subsequent development of cognitive impairment [7], as has volume loss of the amygdala and hippocampus [8]. In sum, studies conducted in adults has shown that diminished brain volume, and architectural damage at the cellular level via microvascular disease, contribute to cognitive loss. In thinking through the circumstances in sub-Saharan Africa which may lead to cognitive loss, it is important that this central pathophysiological mechanism be considered. As outlined below, the iconic illnesses we discuss below are likely to all affect cognition through this well understood set of pathways.

A consequence of this is that the biological plausibility for these illnesses being relevant is quite high.

Once cognitive impairment is present, care of the individual includes the prevention of infectious disease which becomes more common as dementia progresses. These include influenza and pneumococcal disease, urinary tract infections, good oral hygiene to reduce the risk of aspiration pneumonia, and skin integrity to prevent cellulitis and bedsores. This adds to the burden of disease and expenses related to care of the affected individual. Although this is not the focus of our chapter, the spectrum of such conditions may also differ between Western countries and Africa, and childhood infections, vaccinations, and immunological experience may prove important.

Prevention and treatment of cognitive loss is still an evolving topic. Dietary interventions such as the consumption of fruits and vegetables with high levels of anti-oxidants, omega(n)-3 (or ω-3) fatty acids, low intake of saturated fats, moderate alcohol intake, and regular exercise are believed to reduce the risk of cognitive loss by acting against a number of the underlying causal conditions, such as metabolic syndrome or diabetes. A systematic review by Plassman et al. [9] examined studies of factors in five domains: nutritional; medical, social, economic or behavioral; toxic environmental exposures; and genetic. They identified the consumption of ω-3 fatty acids, vegetables and a Mediterranean diet, physical exercise, and cognitive engagement as having at least some level of supportive evidence as ways to reduce risk. (We note that many vegetables and components of the Mediterranean diet contain alpha-linoleic acid (ALA), which can be converted to eicosapentaenoic acid (EPA) and docaosahexaenoic acid (DHA), which are the two ω-3 fatty acids found in fatty fish). Recent studies of cognitive impairment in children in high-income countries have tended to focus on the adverse effects of the heavy metal lead (Pb); social neglect and abuse; and childhood chemotherapy. We note that heavy metal contamination is frequently present in both high and low-income countries, and (for example) that there is no "safe" level of exposure to lead since even low levels of lead exposure can lead to permanent cognitive damage [10, 11]. However, in low and middle income countries, such as Uganda, other threats to childhood cognition exist. These include specific dietary deficiencies such as iron deficiency anemia, early childhood stunting, and other forms of undernutrition, as well as diseases such as malaria. Over 160 million children globally are stunted, and iron-deficiency anemia is one of the most common nutritional disorders. Murray and colleagues estimated in 2012 that 207 million cases of malaria occurred, primarily in pregnant women and children in sub-Saharan Africa [12] There are well documented effects of anemia on cognition; stunting is accompanied by microcephaly (abnormally low brain volume) and decreased synaptic complexity; and both severe and asymptomatic malaria are now being linked to adverse cognitive outcomes.

We believe a common thread relates brain development in utero and in early childhood to adult cognition and to the preservation of cognitive function in old age. We posit that combatting common childhood conditions, such as those outlined

below, will lead to improved adult cognition and productivity. This, in turn, will decrease the risk that these individuals, as adults, will suffer from premature and age-associated cognitive declines given their improved brain reserves.

Stunting, Environmental Enteropathy, and the Gut Microbiome

Stunting is a physical manifestation of undernutrition which results in a child's height being 2 standard deviations or more below the median height for the child's age. Stunting is linked to poor cognitive development in childhood and adolescence, diminished motor development, and lower IQ. Stunted children perform less well than normally nourished children in school and demonstrate poorer cognition. In general, stunted children receive fewer years of schooling and demonstrate less productivity once they achieve adulthood [13–16]. Risk factors for stunting are many – they include undernutrition of the pregnant mother; inadequately nutritious diets; a lack of exclusive breast feeding and socio-economic status and wealth; poor water and sanitation; and many other factors which have been summarized in the recent 2013 *Lancet* series [17, 18]. New to the discussion of causality is the gut microbial community, or the gut microbiota. This community forms a 'microbiome,' or ecological community which contains both normal and pathogenic organisms. (Strictly speaking, the microbiome is the collective genomic structure of the microbiota, but the terms are sometimes used interchangeably). The gut microbiome of normal children is distinctly different from that of malnourished or obese children, and is influenced by environmental exposures.

The presence of stunting is assessed by measuring a child's height (or length) and matching the measured height for age to that of a reference population of normally nourished children of the same age. Given the normal Gaussian variation of height, one expects 95.45 % of children to be within 2 standard deviations of the mean, and ~2.275 % of normal children to meet the definition of stunted. Similarly, 99.73 % of children should be within 3 standard deviations of the mean, with only 0.135 % of normal children having a height for age score 3 deviations below the mean. (The latter is the definition for severe stunting). The Uganda Demographic and Health Survey (DHS) conducted in 2011, however, reported that 33 % of Ugandan children under 5 years of age are stunted, and 14 % are severely stunted [19].

Stunting is accompanied by microcephaly, defined as an head circumference 2 or more standard deviations below the age-adjusted mean. Microcephaly is related to reduced brain volume. Brain growth is most rapid during the last trimester of pregnancy and the first year of life. Malnutrition results in smaller brain size, decreased brain myelinization, DNA and neurotransmitter content, and less cortical dendritic growth [20–22]. Prospective birth cohort data from diverse sites around the world

have shown consistent relationships between early childhood stunting, and decreased cognition, worse economic productivity and achievement, and adult health outcomes [23–25]. It is difficult to imagine a disorder more ripe for attention that childhood stunting when it comes to adult cognition.

Transgenerational effects of stunting have been identified. The adverse effects appear early and continue into adulthood. For example, stunted girls grow up to become short women. Their birth canals are proportionately smaller, and the risk of obstructed labor increases as maternal height declines. In some countries, a practice of "eating down" (moderating food intake) in pregnancy exists, in recognition than a larger baby will cause a more difficult delivery, especially in the setting of small maternal size [26]. Maternal height is inversely associated with child mortality, stunting, underweight and wasting, based upon an analysis of 109 DHS surveys conducted in 54 low and middle income countries [27]. This study included data of 2,661,519 children born to 751,912 mothers after exclusion of outliers or incomplete case records. For every 1 cm increase in height, the risks of these outcomes significantly decreased. Short stature mothers (<145 cm) had a ~40 % greater risk of a child dying than women >160 cm, and the prevalence of stunting and underweight was doubled in the offspring of the shortest group *after* adjustment for confounding variables such as socioeconomic and educational variables.

Maternal overweight and obesity is becoming more common globally just as childhood overweight and obesity, and these appear linked, almost paradoxically, to early childhood undernutrition via epigenetic programming, a form of metabolic imprinting [28, 29]. By this we mean that nutritional gaps in utero predispose the stunted infant to permanent changes in homeostatic mechanisms which favor the later development diabetes, obesity, and the metabolic syndrome [30, 31]. For example, in support of this thesis, low birth weight infants are at elevated risk of childhood insulin resistance [25, 32], an hallmark of diabetes and metabolic syndrome, and hypertension and plasma triglycerides, after adjustment for current size of the child at 9–10 years of age [33]. This form of permanent adaptation to the conditions suffered in utero or in early childhood differs from accommodative adaptation, where a person's metabolism changes to fit a temporary situation and eventually reverts back to a prior set point.

How, then, do these relate to environmental enteropathy and the intestinal microbiome? Scientists is the 1960s and 1970s identified a condition first termed tropical and then environmental enteropathy (EE), as it is widely prevalent in tropical countries where environmental contamination is ubiquitous [34, 35] (Yet another term has been proposed, "acquired environmental enteric dysfunction" [36]). It is characterized by asymptomatic villous atrophy, affecting nutrient absorption, and an inflamed, leaky intestine. This enteric dysfunction is characterized by increased caloric needs to maintain growth, the chronic anemia seen with inflammatory conditions, and increased gut permeability. In a series of landmark studies, Lunn and other co-workers in the 1990s showed that the single best predictor of stunting was gut permeability – an hallmark of EE [37]. Current thinking is that constant exposure to fecal-oral contamination, and repeated episodes of infectious gastroenteritis, "lead to a perpetual state of small bowel injury" [38]. Humphrey cogently synthesized

this work going back to the 1960s forward and developed a simple yet accurate story line: EE is caused by pathogenic fecal bacteria ingested by young children living in unsanitary conditions [39]. In turn, the elevated metabolic demands of enteropathy and state of chronic inflammation lead to growth retardation, potentially through inflammation-mediated inhibition of the growth factor-insulin-like growth factor axis [40]. Recent cross-sectional data from Bangladesh shows significant relationships between fecal environmental contamination (based upon water testing and an household inspection), the presence of environmental enteropathy, and stunting [41]. The implication is clear: protect young children from the fecally contaminated environment, and you prevent stunting and other forms of malnutrition, and potentially the adverse adult consequences as well [42]. One needs clean water and sanitation – toilets – to accomplish this.

The final piece to this evolving picture is the discovery that the microbiome of malnourished children is not only abnormal, it can even promote malnutrition. Smith et al. in 2013 [43] reported on studies in 317 genetically-identical twin pairs in Malawi where one twin was normally nourished and the other had kwashiorkor, a form of stunting that includes body edema (a puffiness from fluids that leak out of the blood vessels and are not reabsorbed). The microbiomes of the normal and malnourished twins were markedly different, and in the case of the malnourished children less mature (the microbiota changes as a child gets older). Furthermore, nutritional supplements designed to rehabilitate the malnourished children helped them gain weight but did not change their microbiomes. Shockingly, when the microbiomes of malnourished children were transferred into germ free mice fed a Malawian diet, the mice lost ~ a third of their body weight in 18 days. In contrast, the transplanted microbiomes of their better nourished siblings did not cause any weight loss in mice. Metabolic analysis suggest that *Biophilia wadsworthia,* a sulfur-consuming bacterium found in the altered microbiota of malnourished children, consumes sulfur-containing amino acids which are already deficient in their diets. (This common anaerobic organism in the human microbiota is the only known intestinal organism to use taurine, a derivative of the amino acid cysteine, as its source for sulphite, its final electron acceptor for respiration. Taurine is essentially absent from vegan diets) [44]. Along the same lines, they found evidence that the microbiome was selectively interfering in the harvesting of dietary energy via the aerobic Krebs citric acid (tricarboxylic acid, TCA) cycle. Because it is well established that our gut flora reflects both our diet and our environment, we posit that an adequate diet and clean environment should prevent this circumstance.

In summary, we see that stunting is the product of under-nutrition (of both the mother and the child), specific poor feeding practices and micronutrient deficits, a lack of clean water and sanitation, the development of environmental enteropathy and the presence of an abnormal microbiome. It is of no little interest that obesity is associated with an abnormal microbiome, which if replaced through a fecal transplant leads to improved insulin sensitivity. Metabolic syndrome, diabetes, and obesity are characterized by low-grade inflammation, as well as increased gut permeability (reviewed in Shen et al. 2013) [45]. Figure 7.2 relates these findings to the microbiomes of normal and obese individuals.

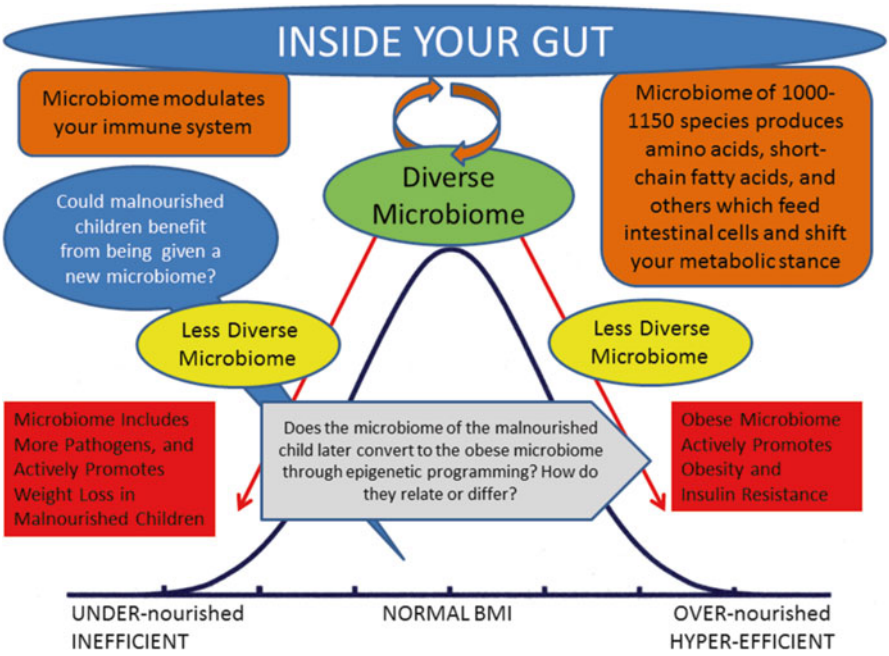

Fig. 7.2 The gut microbiome contributes to both stunting and obesity, which may be related through epigenetic programming. Both the malnourished and obese microbiomes are less diverse than the microbiomes of normally nourished individuals

Iron-Deficiency Anemia (IDA)

Anemia is one of the leading nutritional disorders globally, and the third largest cause of disability. The majority of anemia in children is due to iron deficiency, often compounded by infectious diseases such as malaria and hookworm infection which either destroy or consume red blood cells [46]. It has been repetitively identified as a predictor of decreased cognitive performance [47]. A number of studies have identified iron deficiency anemia (IDA) in infancy and childhood as long-term predictors of decreased cognition, even if treated with iron supplementation (reviewed in Beard and Connor 2003) [48]. Iron is required for brain myelinization, neurotransmitter (gamma-aminobutyric acid, GABA) metabolism, and oxygen delivery to the brain. Children with IDA have cognitive and motor deficits and delayed socio-emotional and neurophysiologic development compared to children without IDA (reviewed in Lozoff et al. 2006) [49]. The majority, but not all, of studies assessing cognition before and after treatment with iron have reported persistent deficits as well.

In an important long-term study of Costa Rican children, 185 children were identified between the ages of 12 and 23 months. Iron status was assessed and all children received iron therapy, with uniformly excellent responses and resolution of anemia.

However, formerly IDA children tested in adolescence and at 19 years of age had persistent motor impairment, need for school grade repetition, depression and anxiety, inattention, impaired executive function, and longer visual-evoked potential latency times when compared to peers who had not had IDA [50, 51]. Dramatically, in the low socioeconomic group, mean IQ was 70.4 in those who had had chronic IDA versus 95.3 in those without IDA. In middle-class children, the respective IQ scores were 93.1 versus 102.8. No evidence of a "catch-up" in cognition was visible for children with chronic iron deficiency in infancy *despite* iron repletion at the time of study enrollment.

Iron deficiency anemia can be prevented in many ways. These include a diet with sufficient iron and the other necessary cofactors required for its uptake, iron fortification of staple foods, and the prevention or treatment of diseases such as malaria and hookworm.

Malaria

Cerebral malaria is a severe neurological manifestation of infection with *Plasmodium falciparum*, the causative agent of falciparum malaria. Coma and seizures are both hallmarks of cerebral malaria. In Uganda, infection with this species of malaria parasite is the most common form of malaria [52]. Unlike other species of malaria, falciparum parasites developing in parasitized red blood cells (pRBCs) attach to endothelial cells lining the vasculature in a process called sequestration. This can lead to reduced local brain perfusion, depriving brain cells of glucose and oxygen, in multiple small areas of the brain. The adherence of pRBCs induces inflammatory changes including cytokine release, endothelial cell activation and death of nearby endothelium, neurons and glia [53]. The blood-brain barrier can be disrupted, and intracranial hypertension is common. Both cerebral malaria, and severe malarial anemia, have now been linked to long-term cognitive impairment as assessed at 1 year after hospitalization in studies conducted in Uganda [54]. Epilepsy develops in about 10 % of children, sometimes after a number of years, and the cumulative incidence increases over time [55]. Severe malaria is also associated with acquired language disorders in a similar percentage (~12 %) of survivors [56].

These can be explained by focal brain injuries (e.g. by causing ischemic neuronal injuries with epileptogenic foci developing, or with focal damage to language centers) but it is possible that they are simply within the spectrum of manifestations of diffuse brain injury. There is a paucity of literature on long-term sequelae of cerebral malaria. We nonetheless posit that a disease this damaging to the brain is likely to contribute to later early loss of cognitive skills through a reduction in brain reserves.

Compounding concerns about the influence of malaria on cognition are recent studies reporting cognitive impairment in children with *asymptomatic* malaria. For example, Ugandan schoolchildren with asymptomatic malaria had lower test scores for sustained attention and abstract reasoning compared to uninfected children [57]. Similar effects have noted in Mali and Yemen [58, 59]. In a year-long prospective

randomized controlled trial conducted in Sri Lanka, children who received antimalarial prophylaxis had reduced malaria and absenteeism, and scored better in both language and mathematics. Educational attainment was significantly related to compliance with the prophylaxis [60]. Another study from Zambia found an association in ~6 year old children (born in 2004) between parasite exposure in 2006 and decreased coping with cognitive tasks and socio-emotional development in 2010 [61]. The control and elimination of malaria should be of concern to those focused on cognition in children, adults and the elderly.

Summary

We have briefly outlined some of the top-tier threats to adult cognition which can be addressed during pregnancy, infancy and childhood. Given the many hundreds of millions of people who are risk of, or already have, anemia, malaria, or stunting, the benefits of preventing or treating these diseases are undoubtedly of large magnitude. We believe there are strong, biologically plausible reasons to link these childhood disorders with adverse cognitive outcomes not only in early adulthood, but also in older adults and the elderly. As the global epidemics of obesity, metabolic syndrome, and hypertension expand to low-income countries like Uganda, we can identify a scientific and social policy agenda which can break the cycles of undernutrition and disease in children which also addresses these new adult scourges.

References

1. Schiepers OJ, et al. APOE E4 status predicts age-related cognitive decline in the ninth decade: longitudinal follow-up of the Lothian Birth Cohort 1921. Mol Psychiatry. 2012;17:315–24.
2. Tishkoff SA, Verrelli BC. Patterns of human genetic diversity: implications for human evolutionary history and disease. Annu Rev Genomics Hum Genet. 2003;4:293–340.
3. Campbell CC, Tishkoff SA. African genetic diversity: implications for human demographic history, modern human origins, and complex disease mapping. Annu Rev Genomics Hum Genet. 2008;9:403–33.
4. Zimmet P, Alberti KGMM, Shaw J. Global and societal implications of the diabetes epidemic. Nature. 2001;414:782–7.
5. Ma RC, Chan JC. Type 2 diabetes in East Asians: similarities and differences with populations in Europe an the United States. Ann N Y Acad Sci. 2013;1281:64–91.
6. Mbanya JC, Motala AA, Sobngwi E, Assah FK, Enoru ST. Diabetes in sub-Saharan Africa. Lancet. 2010;375:2254–66.
7. Bigler EK, Tate DF. Brain volume, intracranial volume, and dementia. Invest Radiol. 2001;36:539–46.
8. den Heijer T, Geerlings MI, Hoebeek FE, Hofman A, Koudstaal PJ, Breteler MMB. Use of hippocampal and amygdalar volumes on magnetic resonance imaging to predict dementia in cognitively intact elderly people. Arch Gen Psychiatry. 2006;63:57–62.
9. Plassman BL, et al. Systematic review: factors associated with risk for and possible prevention of cognitive decline in later life. Ann Intern Med. 2010;153:182–93.

10. Olewe T, Mwanthi MW, Wang'ombe JK, Griffiths JK. Blood lead levels and potential environmental exposures among children under five years in Kibera slums, Nairobi. East Afr J Public Health. 2009;6:6–10.
11. Advisory Committee on Childhood Lead Poisoning Prevention of the Centers for Disease Control and Prevention. Low level lead exposure harms children: a renewed call for primary prevention. Available at: http://www.cdc.gov/nceh/lead/acclpp/final_document_010412.pdf (2012). Accessed 4 Jan 2012.
12. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095–128.
13. Martorell R, Rivera J, Kaplowitz J, Pollitt E. Long term consequences of growth retardation during early childhood. In: Hernandez M, Argenta J, editors. Human growth: basic and clinical aspects. Amsterdam: Elsevier; 1992. p. 143–9.
14. Mendez MA, Adair LS. Severity and timing of stunting in the first two years of life affect performance on cognitive tests in late childhood. J Nutr. 1999;129:1555–62.
15. Ivanovic DM, Perez HT, Olivares MD, Diaz NS, Leyton BD, Ivanovic RM. Scholastic achievement: a multivariate analysis of nutritional, intellectual, socioeconomic, sociocultural, familial, and demographic variables in Chilean school-aged children. J Nutr. 2004;20:878–89.
16. Victora CG, Adair L, Fall C, Hallal PC, Martorell R, Ritcher L, Sachdev HS. Maternal and child undernutrition: consequences for adult health and human capital. Lancet. 2008;371:340–57.
17. Bhutta ZA, Das JK, Rizvi A, et al. The Lancet Nutrition Interventions Review Group, The Maternal and Child Nutrition Study Group. Evidence based interventions for improvement of maternal and child nutrition: what can be done and at what cost? Lancet 2013; published online June 6. http://dx.doi.org/10.1016/S0140-6736(13)60996-4
18. Ruel M, Alderman H, The Maternal and Child Nutrition Study Group. Nutrition-sensitive interventions and programmes. Lancet 2013; published online June 6. http://dx.doi.org/10.1016/S0140-6736(13)60843-0
19. Uganda Bureau of Statistics (UBOS), ICF International Inc. Uganda Demographic and Health Survey 2011. Kampala/Maryland: UBOS and Calverton/ICF International Inc. Available at: http://www.ubos.org/onlinefiles/uploads/ubos/UDHS/UDHS2011.pdf (2012).
20. Winick M, Brasel JA. Early malnutrition and subsequent brain development. Ann N Y Acad Sci. 1977;300:280–2.
21. Winick M, Rosso P. Head circumference and cellular growth of the brain in normal and marasmic children. J Pediatr. 1969;74:774–8.
22. Winick M. Prenatal protein-calorie malnutrition and brain development. Prog Clin Biol Res. 1985;163B:397–402.
23. Martorell R, Horta BL, Adair LS, Stein AD, Richter L, Fall CHD, Bhargava SK, Biswas SKD, Perez L, Barros FC, Victora CG, Consortium on Health Oriented Research in Transitional Societies (COHORTS) Group. Weight gain in the first two years of life is an important predictor of schooling outcomes in pooled analyses from five birth cohorts from low- and middle-income countries. J Nutr. 2010;140:348–54.
24. Veena SR, Krishnaveni GV, Wills AK, Kurpad AV, Muthayya S, Hill JC, Karat SC, Nagarajaiah KK, Fall CHD, Srinivasan K. Association of birthweight and head circumference at birth to cognitive performance in 9–10 year old children in south India: prospective birth cohort study. Pediatr Res. 2010;67:424–9.
25. Adair LS, Fall CHD, Osmond C, Stein AD, Martorell R, Ramirez-Sea M, Sachdev HS, Dahly DL, Bas I, Norris SA, Micklesfield L, Hallal P, Victora CG, for the COHORTS Group. Associations of linear growth and relative weight gain during early life with adult health and human capital in countries of low and middle income: findings from five birth cohort studies. Lancet. 2013;382(9891):525–34.
26. Bhat D, Troy L, Karim R, Levinson FJ. Determinants of food consumption during pregnancy in rural Bangladesh. Bangladesh Dev Stud. 2002;28:95–104.

27. Özaltin E, Hill K, Subramanian SV. Association of maternal stature with offspring mortality, underweight, and stunting in low- to middle-income countries. JAMA. 2010;303(15): 1507–16.
28. Keino S, Plasqui G, Ettyang G, van den Borne B. Determinants of stunting and overweight among young children and adolescents in sub-Saharan Africa. Food Nutr Bull. 2014;35(2):167–78.
29. Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, de Onis M, Ezzati M, Grantham-McGregor S, Katz J, Martorell R, Uauy R, The Maternal and Child Nutrition Study Group. Maternal and child undernutrition and overweight in low-income and middle-income countries. Lancet. 2013;382:427–51.
30. Gallou-Kabani C, Junien C. Nutritional epigenomics of metabolic syndrome: new perspective against the epidemic. Diabetes. 2005;54:1899–906.
31. Martorell R, Zongrone A. Intergenerational influences on child growth and undernutrition. Paediatr Perinat Epidemiol. 2012;26(S1):302–14.
32. Lawlor DA, Riddoch CJ, Page AS, Anderssen SA, Froberg K, Harro M, Stansbie D, Smith GD. The association of birthweight and contemporary size with insulin resistance among children from Estonia and Denmark: findings from the European Youth Heart Study. Diabet Med. 2005;22(7):921–30.
33. Krishnaveni GV, Veena SR, Wills AK, Hill JC, Karat SC, Fall CHD. Adiposity, insulin resistance and cardiovascular risk factors in 9–10-year-old Indian children: relationships with birth size and postnatal growth. J Dev Orig Health Dis. 2010;1(6):403–11.
34. Baker SJ, Mathan VI. Tropical enteropathy and tropical sprue. Am J Clin Nutr. 1972;25:1047–55.
35. Fagundes-Neto U, Viaro T, Wehba J, Patricio FR, Machado NL. Tropical enteropathy (environmental enteropathy) in early childhood: a syndrome caused by contaminated environment. J Trop Pediatr. 1984;30:204–9.
36. Keusch GT. Implications of acquired environmental enteric dysfunction for growth and stunting in infants and children living in low- and middle-income countries. Food Nutr Bull. 2013;34:357–61.
37. Lunn PG, Northrop-Clewes CA, Downes RM. Intestinal permeability, mucosal injury, and growth faltering in Gambian infants. Lancet. 1991;338:907–10.
38. Korpe PS, Petri WA. Environmental enteropathy: critical implications of a poorly understood condition. Trends Mol Med. 2012;18(6):328–36.
39. Humphrey JH. Children undernutrition, tropical enteropathy, toilets, and handwashing. Lancet. 2009;374:1032–5.
40. Prendergast AJ, Rukobo S, Chasekwa B, Mutasa K, Ntonzini R, et al. Stunting is characterized by chronic inflammation in Zimbabwean infants. PLoS One. 2014;9(2):e866928.
41. Lin A, Arnold BF, Afreen S, Goto R, Huda TMN, Haque R, Raqib R, Unicomb L, Ahmed T, Colford Jr JM, Luby SP. Household environmental conditions are associated with enteropathy and impaired growth in rural Bangladesh. Am J Trop Med Hyg. 2013;89(1):130–7.
42. DeBoer MD, Lima AAM, Oría RB, Scharf RJ, Moore SR, Luna MA, Guerrant RL. Early childhood growth failure and the developmental origins of adult disease: do enteric infections and malnutrition increase risk for the metabolic syndrome? Nutr Rev. 2012;70:642–53.
43. Smith MI, Yatsunenko T, Manary MJ, Trehan I, Mkakosya R, Cheng J, et al. Gut microbiomes of Malawian twin pairs discordant for kwashiorkor. Science. 2013;339:548–54.
44. Carbonero F, Benefiel AC, Alizadeh-Ghamsari AH, Gaskins HR. Microbial pathways in colonic sulfur metabolism and links with health and disease. Front Physiol. 2012;3:448.
45. Shen J, Obin MS, Zhao L. The gut microbiota, obesity and insulin resistance. Mol Aspects Med. 2013;34:39–59.
46. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis fo the Global Burden of Disease Study 2010. Lancet. 2012;380:2163–96.

47. Kordas K, Lopez P, Rosado JL, Vargas GG, Rico JA, Cebria'n ME, Stoltzfus RJ. Blood lead, anemia, and short stature are independently associated with cognitive performance in Mexican school children. J Nutr. 2004;134:363–71.
48. Beard JL, Connor JR. Iron status and neural functioning. Annu Rev Nutr. 2003;23:41–58.
49. Lozoff B, Beard J, Connor J, Felt B, Georgieff M, Schallert T. Long-lasting neural and behavioral effects of iron deficiency in infancy. Nutr Rev. 2006;65(5 Pt 2):S34–91.
50. Lozoff B, Jimenez E, Hagen J, et al. Poorer behavioral and developmental outcome more than 10 years after treatment for iron deficiency in infancy. Pediatrics. 2000;105:E51. Available at: http://www.pediatricsorg/cgi/content/full/105/4/e51. Accessed 3 Oct 2006.
51. Lozoff B, Jimenez E, Smith JB. Double burden of iron deficiency and low socio-economic status: a longitudinal analysis of cognitive test scores to 19 years. Arch Pediatr Adolesc Med. 2006;160(11):1108–13.
52. Uganda Bureau of Statistics (UBOS), ICF International Inc. Uganda Demographic and Health Survey 2011. Kampala/Maryland: UBOS and Calverton/ICF International Inc. Available at: http://www.ubos.org/onlinefiles/uploads/ubos/UDHS/UDHS2011.pdf (2012).
53. Idro R, Marsh K, John CC, Newton CRJ. Cerebral malaria: mechanisms of brain injury and strategies for improved neurocognitive outcome. Pediatr Res. 2010;68:267–74.
54. John CC, Bangirana P, Byarugaba J, Opoka RO, Idro R, Jurek AM, Wu B, Boivin MJ. Cerebral malaria in children is associated with long-term cognitive impairment. Pediatrics. 2008;122:e92–9.
55. Opoka RO, Bangirana P, Boivin MJ, John CC, Byarugaba J. Seizure activity and neurological sequelae in Ugandan children who have survived an episode of cerebral malaria. Afr Health Sci. 2009;9:75–81.
56. Carter JA, Lees JA, Gona JK, Murira G, Rimba K, Neville BG, Newton CR. Severe falciparum malaria and acquired childhood language disorder. Dev Med Child Neurol. 2006;48:51–7.
57. Nankabirwa J, Wandera B, Kiwanuka N, Staedke SG, Kamya MR, Brooker SJ. Asymptomatic *Plasmodium* infection and cognition among primary schoolchildren in a high malaria transmission setting in Uganda. Am J Trop Med Hyg. 2013;88(6):1102–8.
58. Thuilliez J, Sissoko MS, Toure OB, Kamate P, Berthelemy JC, Doumbo OK. Malaria and primary education in Mali: a longitudinal study in the village of Doneguebougou. Soc Sci Med. 2010;71:324–34.
59. Al Serouri AW, Grantham-McGregor SM, Greenwood B, Costello A. Impact of asymptomatic malaria parasitemia on cognitive function and school achievement of schoolchildren in the Yemen Republic. Parasitology. 2000;121:337–45.
60. Fernando D, de Silva D, Carter R, Mendis KN, Wickremasinghe R. A randomized, double-blind, placebo-controlled, clinical trial of the impact of malaria prevention on the educational attainment of school children. Am J Trop Med Hyg. 2006;74(3):386–93.
61. Fink G, Olgiati A, Hawela M, Miller JM, Matafwali B. Association between early childhood exposure to malaria and children's pre-school development: evidence from the Zambia early childhood development project. Malar J. 2013;12:12.

Chapter 8
Strokes as Seen in Mulago Hospital, Uganda

Stephen Muwonge Matovu and Robert Mukisa

Abstract This chapter examines stroke as the leading cause of admission, disability and death in the Neurology unit at Mulago National Referral Hospital in Uganda. Patients are either referred from a primary health care center or present directly to the hospital. There is an increasing burden of stroke patients in the inpatient wards, outpatient clinic and the physiotherapy departments. This is because the population is undergoing a rapid epidemiological transition with increased exposure to, and development of, stroke risk factors, together with aging of the population. The clinical presentation of stroke, management and rehabilitation are discussed. Community awareness of the four preventative strategies of stroke, improved stroke care in the Neurology unit and rehabilitation are cornerstones in mitigating the stroke burden and its antecedent complications. This chapter, however, will mostly report on preliminary studies undertaken in Mulago hospital, Uganda to elucidate the burden of stroke at this tertiary care facility as there is a paucity of studies on the subject of stroke in Uganda.

Keywords Stroke burden • Risk factors • Stroke complications • Mulago hospital

Introduction

Stroke is defined as rapidly developing clinical signs of focal (or global) disturbance of cerebral dysfunction with symptoms lasting 24 h or longer or leading to death with no apparent cause other than that of vascular origin [1]. Stroke is thus a term that is used to describe brain injury caused by an abnormality of the blood supply to a part of the brain.

Stroke is a relatively common presenting diagnosis to Mulago National Referral Hospital with the number of patients being admitted with stroke on the Neurology unit being on the increase. Between June and October 2011, 206 patients with stroke

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S. Musisi, S. Jacobson (eds.), *Brain Degeneration and Dementia in Sub-Saharan Africa*, DOI 10.1007/978-1-4939-2456-1_8

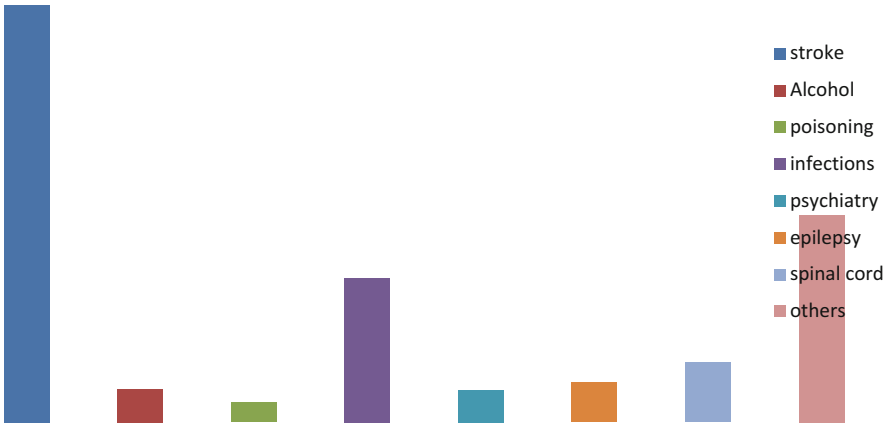

Fig. 8.1 Disease burden on the neurology unit in Mulago Hospital, 2012 (Matovu et al. 2012 data unpublished)

were admitted compared to only 109 in 2005 and 60 in 1999 during the same months period [2]. Stroke is thus the leading cause of admission on the Neurology Unit at Mulago National Referral Hospital (Fig. 8.1).

Risk Factors for Stroke

In a study carried out in Uganda's Mulago National Referral hospital, in Kampala, Nakibuuka et al. [3] investigated the main risk factors for ischemic and hemorrhagic stroke. The parameters noted were past medical history, physical examination findings, key laboratory investigations and Ultrasonography investigations. Table 8.1 below shows the main findings.

For both types of stroke (ischemic and hemorrhagic), the outstanding risk factors for stroke were Hypertension (BP > 140/90 mmHg), physical inactivity, alcoholism, dyslipidemias, Diabetes Mellitus, arthrosclerosis and a positive syphilis serology.

Hypertension

More than 50 % of patients with either ischemic or hemorrhagic stroke reported a history of hypertension, in which more than half of the patients were found to have a blood pressure greater than 140/90 mmHg. Of these patients, however, 27 (32 %) patients reported sporadic use of anti-hypertensive medications, with only 7 patients (8 %) reporting regular medication use. Only 3 patients reported regular use of aspirin prophylaxis for stroke, and these all presented with ischemic stroke.

Table 8.1 Risk factors of stroke among patients admitted to Mulago National Referral Hospital in 2012

Risk factor	Percentage of patients	Percentage of patients
	With ischemic stroke (N = 66)	**With hemorrhagic stroke (N = 19)**
I. Past medical history		
Hypertension	57.6	68.4
Physical inactivity	40.9	36.8
Diabetes mellitus	12.1	5.2
Current smoking	7.6	5.2
Alcohol	18.2	21.1
II. Examination findings		
Irregularly irregular pulse	22.7	5.3
Systolic BP >140 mmHg	47.0	73.7
Diastolic BP >90 mmHg	36.4	68.4
III. Laboratory findings		
Total cholesterol >200 mg/dl	31.0	39.0
LDL cholesterol >110 mg/dl	43.1	33.3
HDL cholesterol <40 mg/dl	38.0	17.0
Triglycerides >150 mg/dl	23.1	33.3
FBS >126 mg/dl	43.1	55.6
Reactive TPHA	26.2	50.0
Reactive HIV serology	7.7	0
IV. Ultrasound findings		
Atherosclerosis on CUS	46.0	46.7

Cardiac Causes: Embolic Source, Atrial Fibrillation and Stenosis

In Nakibuuka's study, 18 patients had a suspected cardio-embolic stroke, with 18.8 % patients found to have an irregularly irregular pulse. However, none of these patients were aware of a previous diagnosis of atrial fibrillation or were taking any medications. Two of these patients were found to have severe valvular heart disease, suggesting that atrial fibrillation could be an important under-recognized cause of stroke in African populations [3–5]. Atherosclerosis in the carotid arteries and cardiac left ventricular hypertrophy were commonly found on physical examination.

Diabetes Mellitus, Dyslipideamias and Lifestyle

Thirty eight patients were found to have a Fasting Blood Sugar (FBS) greater than 126 mg/dl, consistent with a diagnosis of Diabetes Mellitus, but only nine of these patients had a known previous diagnosis of the diabetes. Commonly recognized risk factors, such as hypercholesterolemia, physical inactivity, current smoking and alcohol were frequently found in this stroke victim population.

Syphilis and Human Immunodeficiency Virus

Twenty six patients were found to have reactive serology for syphilis, and only five patients were found to have HIV diagnosed by Abbot test. All these patients were on treatment for these disorders.

Socio-demographic Associations of the Stroke Victims Seen at Mulago Hospital

In terms of their sociodemographic characteristics, Nakibuuka et al. [3] found that the stroke victims were almost of equal gender representation with 51.8 % females but they had a bimodal age distribution with a peak in the 40–49 year age group (22.4 %) and in those aged 60–80 years (37.6 %). Generally, stroke was more common in older individuals and the mean age for all stroke patients was 62.2 years with the vast majority of them being above 40 years old (83.5 %). Most were married (61.2 %), had primary school education or below (54.1 %) and were employed (52.9 %) as shown in Table 8.2 below. These findings were similar to the findings of studies done in other African countries in Zimbabwe [6, 7].

Table 8.2 Socio demographic characteristics of stroke patients admitted to Mulago National Referral Hospital

Characteristics	Number (N = 85)	Percentage (%)
Age (years)		
20–29	8	9.4
30–39	6	7.1
40–49	19	22.4
50–59	11	12.9
60–69	16	18.8
70–79	16	18.8
80+	9	10.6
Gender		
Female	44	51.8
Highest education level attained		
Never been to school	14	16.5
0–7 years	32	37.6
8–12 years	23	27.1
More than 12 years	16	18.8
Marital status		
Never married	6	7.1
Married	52	61.2
Divorced	17	20.0
Widowed	10	11.8

(continued)

Table 8.2 (continued)

Characteristics	Number (N = 85)	Percentage (%)
Occupation		
Student	3	3.5
Unemployed	37	43.5
Employed	45	52.9

Table 8.3 Incidence of ischemic and hemorrhagic stroke according to gender and age group as seen at Mulago Hospital[a]

	Ischemic stroke						Hemorrhagic stroke			
	Male N = 35			**Female N = 31**			**Male (n = 9)**		**Female N = 10**	
Age (years)	AS	CE	O	AS	CE	O	IPH	SAH	IPH	SAH
21–30	0	3	1	0	0	0	0	0	0	0
31–40	1	0	0	0	0	3	1	0	0	0
41–50	2	1	0	1	2	0	1	1	1	1
51–60	7	1	1	1	2	2	1	0	1	1
61–70	3	2	2	5	3	2	2	0	3	0
71+	7	0	4	5	4	1	2	1	3	0
Total	20	7	8	12	11	8	7	2	8	2

[a]*AS* atherosclerotic, *CE* cardio-embolic, *O* other, *IPH* intraparenchymal hemorrhage, *SAH* subarachnoid hemorrhage

Stroke Types

Strokes are divided into two very broad groups namely hemorrhagic strokes and ischemic strokes. In ischemia, there is not enough blood supply to allow continued normal functioning of the affected brain tissue. Brain ischemia is much more common in these than in those due to hemorrhage. About four strokes out of every five are ischemic. In hemorrhage, there are several different subtypes characterized by their locations inside of the skull. Hemorrhages within the brain substance (inside of the pia mater) are called intracerebral hemorrhages. Those between the pia mater and arachnoid are called subarachnoid hemorrhages. Regarding stroke types in Mulago National Referral hospital, 77.6 % were ischemic while 22.4 % were hemorrhagic stroke as confirmed by Computed Tomography scan of the brain. The incidence of both ischemic and hemorrhagic stroke increased with age as seen in Table 8.3 [3]. Mukisa et al. [8] in a separate study done in Mulago National referral hospital, had the same findings with the majority of patients admitted with stroke having ischemic stroke (82.4 %) and those with hemorrhagic stroke were 17.6 %. The observed ratio of ischemic to hemorrhagic stroke of 4:1 was similar to other studies among African populations [9–11]. Atherosclerotic stroke was the commonest ischemic stroke in etiology, being observed in 43.5 % patients with ischemic stroke. Intraparenchymal hemorrhage was the most common hemorrhagic stroke in etiology, in 78.9 % of patients with hemorrhagic stroke [3]. Table 8.3 summarizes these findings.

Clinical Presentation of Stroke

Cerebral Infarction

Here the symptoms reflect the vascular territory involved [12]. Dominant hemisphere stroke (left sided stroke) presents with aphasia, left gaze deviation (preference), right visual field deficit, right hemiparesis and right hemisensory loss. Non-dominant hemisphere stroke (right sided stroke) presents with left hemi-inattention, right gaze deviation (preference), left visual field deficit, left hemiparesis and left hemisensory loss. In Intracerebral haemorrhage, symptoms may progress over the first several hours as the haematoma expands. Vomiting may occur in most cases [13].

Brainstem involvement presents with diplopia/dysconjugate gaze, gaze deviation, paralysis/paresis of vertical eye movement, vertigo/tinnitus, nystagmus, Horner's syndrome, dysarthria, dysphagia, hemiparesis or quadriparesis, sensory loss in hemibody or all four limbs, crossed signs, nausea, vomiting, hiccups, decreased consciousness and abnormal respirations.

Cerebellar involvement presents with truncal/gait ataxia and ipsilateral limb ataxia. Cerebellar haematoma presents with sudden onset of headache, severe ataxia, dysarthria, nystagmus, vertigo and vomiting. Cerebrospinal fluid obstruction hydrocephalus with symptoms and signs of raised intracranial pressure.

Supratentorial haematoma presents with sudden onset of headache followed by either rapid loss of consciousness or a gradual deterioration in conscious level over 24–48 h due to mass effect. Hemiparesis, hemisensory loss and homonymous hemianopia are common. Third nerve palsy indicates transtentorial herniation.

Pontine haematoma presents with sudden loss of consciousness, quadriplegia, respiratory irregularities, slowed respiration, pinpoint pupils, pyrexia, dysconjugate eye movements and death often follows.

Subarachnoid Haemorrhage

Here, the severity of the symptoms is related to the severity of the bleed and symptoms usually continue for many days. Sudden onset of a severe headache, transient or prolonged loss of consciousness or epileptic seizure may immediately follow. Nausea and vomiting are common. A stiff neck may be present after 3–12 h. Bleeding may injure adjacent tissue and produce symptoms such as limb weakness and inability to talk (Braunwald et al. Harrison's 16th edition page 2387).

Clinically, in a review study of admitted stroke patients at Mulago hospital neurology unit, Kwarisiima et al. [14] found that all (100 %) of admitted patients presented with focal neurological deficits with 76 % having motor deficits as the commonest neurological deficit followed by impaired level of consciousness which accounted for 61 % of the admissions. Table 8.4 summarizes these points.

Table 8.4 Clinical presentation of stroke patients admitted in Mulago National Hospital

Sign	Frequency N = 128	Percentage
Sudden trouble in walking	108	84
Sudden weakness of the face	109	85
Sudden numbness of the faces	80	63
Sudden onset of vomiting	37	29
Loss of consciousness	78	61
Motor	97	76
Sensory	2	02
Motor and sensory	29	22
Glasgow coma scale		
<9	38	30
≥9	90	70

Investigations for Stroke at Mulago Hospital

Neuroimaging

Mulago National Referral hospital is Uganda's national referral hospital and therefore a tertiary care hospital. As such the department of Radiology has a Computed Tomography (CT) scan. This enables confirmation of the diagnosis of stroke, establishes the underlying pathology, identifies the size and site of the lesion, and establishes the etiological mechanism. The brain Computed Tomography scan will establish the pathological diagnosis as either infarction or haemorrhage and exclude other conditions that may mimic stroke. In Mulago hospital 28 % of patients presenting with a suspected stroke were found to have a non-stroke diagnosis [3], a value much lower than 43 % found in a study done in Nigeria [15]. Nevertheless, it still emphasizes the relevance of CT scan as gold standard in stroke diagnosis [11, 15, 16] as Table 8.5 below illustrates.

Computed Tomography Appearance

A haemorrhage is seen within a few minutes as an area of increased attenuation (Fig. 8.2). The appearances of an infarct change over the first few weeks, and not all infarcts show up on Computed Tomography scan (Fig. 8.3). Magnetic Resonance Imaging is more sensitive to small areas of ischemia and can detect the traces of old haemorrhage (haemosiderin deposits) indefinitely.

Table 8.5 Non-contrast head CT- scan findings among patients at Mulago Hospital

Non-contrast head CT scan finding	N (%)
Ischemic stroke	66 (52.0)
Hemorrhagic stroke	19 (15.0)
Neoplasm[a]	8 (6.3)
Severe brain atrophy	8 (6.3)
Subdural hematoma[a]	6 (4.7)
Brain abscess[a]	4 (3.1)
Toxoplasmosis	4 (3.1)
Normal repeated CT scan on day 7	3 (2.4)
Intracranial hypertension	3 (2.4)
Extensive calcifications	2 (1.6)
Pan-sinusitis	1 (0.8)
Meningoencephalitis	1 (0.8)
Tuberculosis choroiditis	1 (0.8)
Chronic epidural hematoma[a]	1 (0.8)

[a]Surgically correctable conditions

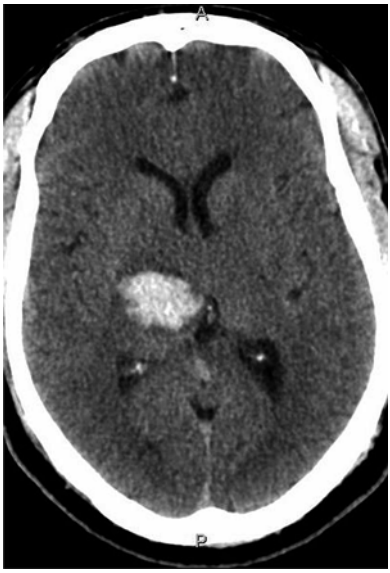

Fig. 8.2 Computed tomography scan showing cerebral haemorrhage

Other Imaging Investigations

Doppler Ultrasound Scans of the Carotid Arteries

Doppler ultrasound scan of the carotid arteries is done at the Uganda Heart Institute, Mulago National Referral Hospital. It detects atherosclerotic plaques, discrete lesions, abnormal velocity flow patterns, irregular flow peaks, occlusion, dissection and evidence of internal carotid artery stenosis.

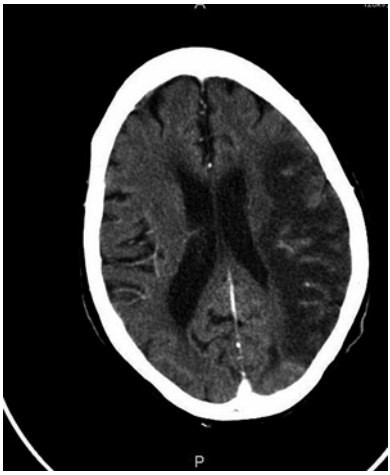

Fig. 8.3 Computed tomography scan showing cerebral ischemia

Cardiac Investigations

These are done at the Uganda Heart Institute, Mulago National Referral Hospital. An Electrocardiogram is used detect atrial fibrillation. Transoesophageal echocardiography is used to identify sources of stroke such as akinetic wall segments, mural thrombi, severe valvular lesions, multiple valvular lesions, valvular vegetations, ventricular ejection fraction of <35 %, an atrial abnormality, ulcerated aortic atherosclerosis or dissection.

Laboratory Investigations in Acute Stroke

The following essential investigations should be done routinely for patients admitted with stroke such as to the Neurology unit in Mulago.

Full blood count: Thos will indicate the presence of polycythaemia, raised white cell count due to infection, thrombocythaemia which increases the risk of infarction and thrombocytopenia which predisposes to haemorrhage

Erythrocyte sedimentation rate: If this is raised, it may indicate infection or Vasculitis

Urea and electrolytes: These are affected by dehydration which may result into hypo perfusion

Fasting blood sugar: Is often raised initially. If it persists then this confirms diabetes mellitus

Syphilis serology: This establishes a diagnosis of meningo-vascular neurosyphilis.

Coagulation profile: This is essential in hemorrhagic stroke and in young patients without identifiable risk factors

Blood cultures: Do this if you suspect bacterial endocarditis
Fasting lipid profile: This detects underlying dyslipideamias
Lumbar puncture: *It h*elps in confirming subarachnoid haemorrhage (xanthochromic), meningitis and encephalitis. Also do a VDRL on it to exclude syphilis

Management

The overall aim of stroke care is to decrease morbidity and mortality, to optimize function recovery and to prevent recurrence of strokes. This is achieved by good nursing care, specific stroke treatment, maintenance of fluid and electrolytes, nutrition, avoiding systemic complications and early rehabilitation.

General Treatment in Caring for Acute Stroke Patients

1. Start with hourly neurological observations and change to 4 hourly if stable. These include:
   - Level of consciousness using Glasgow Coma Scale
   - Vital signs
   - Oxygen saturation
2. Monitor blood glucose. If more than 11 mmol/L start insulin sliding scale
3. Intravenous fluids in dehydrated patients and those unable to swallow
4. Evaluate swallowing after 24 h
   - Observe the patient attempting to swallow using sips of water in upright position
   - Check for coughing or gagging reflexes
   - If swallowing is impaired keep nil per mouth.
   - Continue intravenous fluids for 48 h then start nasogastric tube feeding if still unable to swallow
5. Urinary catheterization if incontinent or in retention
6. Prevent constipation by adequate hydration and laxatives
7. Prevent pressure sores by advising a relative or a care taker to supervise 2 hourly turning
8. Decrease the risk of deep vein thrombosis by using compression stockings in addition to oral aspirin if intracerebral haemorrhage is excluded
9. Treat sepsis and pyrexia with antibiotics and antipyretics respectively
10. Early physiotherapy and mobilize out of bed
11. Occupational, speech and language therapy
12. The family is taught good nursing care/manual handling techniques before discharge home

Specific Treatments

Antiplatelet Drugs

All ischaemic strokes are started on aspirin immediately or as soon as the diagnosis is made followed by long term treatment. Aspirin, when given effectively, prevents deaths, major disability (dependence) and recurrent strokes when used as longer term therapy. The dose is 300 mg per os daily for the first 2 weeks followed by 75–150 mg per os thereafter. Patients that are intolerant of aspirin are treated with either clopidogrel or dipyridamole.

Antihypertensive Drugs

Blood pressure lowering during the first 24–48 h is avoided as an acute drop in blood pressure can reduce perfusion to an already ischaemic brain. Treatment is considered only if the blood pressure is persistently elevated that is ≥180/105 mmHg in ischaemic stroke. Aim at a daily reduction of 10–20 mmHg. In intracerebral haemorrhage treatment is started if the blood pressure is more than 160/100 mmHg. In the acute phase, blood pressure reduction is achieved by treating with sublingual nifedipine and then orally twice daily. For a gradual reduction, use captopril, atenolol or hydrallazine as the alternatives used.

Anticoagulation

Anticoagulants are used in patients with an ischaemic stroke and a cardiac embolic source or atrial fibrillation to prevent further strokes. Patients are first treated with aspirin as anticoagulation is started 2 weeks later after the stroke because of the risk of intracerebral haemorrhage. Warfarin is administered per os in a loading dose of 10 mg daily for 2 days followed by a maintenance dose depending on the prothrombin time or international normalized ratio (INR). The aim is to have and maintain an INR of two to three or a prothrombin time of twice the normal range.

Thrombolysis

Thrombolytic therapy for ischaemic strokes with intravenous recombinant tissue plasminogen activators like alteplase is not possible in Mulago Hospital, because often, the minimum time of admission to Mulago hospital of patients with an acute stroke after its occurrence is 2 days [7]. Thrombolytic agents are only beneficial when administered within 3–6 h after stroke onset at maximum.

Neurosurgery

Evacuation of a cerebellar haematoma is life saving. Evacuation of supratentorial hematomas is done in only younger patients with deteriorating consciousness. Neurosurgery is beneficial for obstructive hydrocephalous following stroke.

Stroke Complications

Stroke patients are at risk for complications which may lead to death. Cerebral edema, progression of the stroke and complications are responsible for the common neurological worsening in the first 48 h.

Acute Complications

The main acute complications are aspiration pneumonia, pulmonary embolism, pressure sores and urinary tract infections. They occur in over 50 % of hospitalized stroke patients and are associated with a poor prognosis. Aspiration pneumonia is the main cause of death in stroke in hospitalized patients. It is frequent in patients with extensive strokes and coma. Management includes avoiding oral intake, chest physiotherapy and use of antibiotics.

Patients with stroke are at significant risk for deep vein thrombosis and pulmonary embolism. The use of low dose aspirin and compression stockings decreases this risk. Pressure sores, spasticity and contractures are common and are reduced by early patient positioning, 2 hourly turning, and passive exercises.

Chronic Complications

These include disability, spasticity, contractures, pain, depression, dementia and late onset seizures. Post stroke depression is common occurring in over 50 % of the patients, especially in right sided stroke. It's treated using tricyclic antidepressants such as Imipramine or selective serotonin reuptake inhibitors such as Fluoxetine.

Dementia after stroke is common and is a major long term cause of dependency, particularly in the elderly [17, 18]. In Mulago hospital the prevalence of cognitive impairment among patients admitted with stroke was found to be 63 % [8]. The mild form was most common representing 27 % of the cases. The cognitively impaired with no dementia were more than those with dementia contributing 43 % and 20 % respectively of the stroke patient study population [8].

Rehabilitation

In Mulago hospital, rehabilitation is one of the most important aspects in the care of stroke patients. The aim is to improve quality of life by reducing emotional, functional, cognitive, physical and communication disorders. Early mobilization and rehabilitation help and improve outcome. This is done on a daily basis on the Neurology unit. Physiotherapy maximizes functional recovery, occupational therapy is necessary for functional assessment and the provision of practical aids. Speech and language therapy helps with aphasia, dysarthria and dysphagia. Psychiatric consultation is routinely done for those found to be depressed.

Prevention of Stroke

Lifestyle Measures

These include the four-by-four action plan approach. (1) Diet entails eating fruits and vegetables, reducing salt, sugar and animal fat intake. (2) Increased physical activity is emphasized as this maintains the ideal body weight. (3) Moderation of alcohol intake and (4) stopping smoking are all important in both primary prevention of stroke at community level and secondary prevention when the stroke/transient ischaemic attack has occurred.

Secondary Prevention

Stroke recurrence occurs in some patients admitted to Mulago hospital and attempts are routinely made to stop this using the following measures:

Antiplatelete Drugs
Low dose daily aspirin 75–150 mg decreases the risk of another ischaemic stroke. Clopidogrel 75 mg daily and dipyridamole are the alternative drugs in patients with aspirin intolerance. Antiplatelet therapy has to be continued indefinitely.

Anticoagulants
All ischaemic stroke patients presenting with atrial fibrillation or mitral valve disease are anticoagulated indefinitely with warfarin with a target International Normalized Ratio of 2.5, as prophylaxis or using aspirin if there is no contraindication to it. The annual risk of embolism with either valvular heart disease or atrial fibrillation is reduced by anticoagulating with warfarin.

Antihypertensives
Treatment of hypertension significantly reduces the risk of strokes. Blood pressure treatment is started in hypertensive stroke patients and continued indefinitely to be monitored on discharge from hospital.

Statins
Cholesterol lowering drugs, simvastatin 20–40 mg per os daily or another statin therapy for raised cholesterol levels prevents stroke in patients with a history of cerebrovascular disease and ischaemic heart disease.

Carotid Stenosis
Asymptomatic carotid stenosis of >70 % and symptomatic stenosis of <70 % are managed medically.

Prognosis

The outcome for stroke patients is poor. The mortality within the first year is over 30 %, with a further one third disabled and about one third regaining independent living. The majority of deaths occur during the first week and month after the stroke and continues throughout the first year.

The 30-day mortality among adult patients with stroke admitted at Mulago hospital is 43.8 % [14]. This is similar to other early stroke case-fatality findings observed in African hospital-based studies [7, 19, 20]. It was significantly associated with older age, leucocytosis, impaired level of consciousness and high body temperature [14].

More patients with subarachnoid haemorrhage or intracerebral haemorrhage die within 30 days than do those with cerebral infarction. The risk of recurrence continues over time.

References

1. WHO MONICA Project. Monitoring trends and determinants in cardiovascular disease: a major international collaboration. J Clin Epidemiol. 1988;41:105–14.
2. Matovu SM, Nakibuuka J, Mukisa R, Musubire A, Kaddumukasa M. Stroke burden on the Neurology Unit in Mulago Hospital, Uganda. 2012.
3. Nakibuuka J, Abwooli N, Namale A, Blondin N, Ddumba E. A descriptive epidemiological study on stroke in Kampala, Uganda: a hospital-based study. Afr J Neurol Sci. 2012;31(1):41–48.
4. Ntep-Gweth M, Zimmermann M, Meiltz A, Kingue S, Ndobo P, Urban P, Bloch A. Atrial fibrillation in Africa: clinical characteristics, prognosis, and adherence to guidelines in Cameroon. Europace. 2010;12(4):482–7.
5. Sliwa K, Wilkinson D, Hansen C, Ntyintyane L, Tibazarwa K, Becker A, Stewart S. Spectrum of heart disease and risk factors in a black urban population in South Africa (The Heart of Soweto Study): a cohort study. Lancet. 2008;371(9616):915–22.
6. Matenga J. Stroke incidence rates among black residents of Harare – a prospective community based study. S Afr Med J. 1997;87:606–9.
7. Rosman KD. Epidemiology of stroke, urban black population. Stroke. 1986;17:667–9.
8. Mukisa R, Ddumba E, Musisi S, Kiwuwa MS. Prevalence and types of cognitive impairment among patients with stroke attending a referral hospital in Uganda. Afr J Neurol Sci. 2011;30(2):56–63.

9. O'donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, Rangarajan S, Islam S, Pais P, INTERSTROKE investigators, et al. Risk factors for ischaemic and intracerebral Haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet. 2010;376:112–23.
10. Onwuchewa A, Bellgam H, Asekomeh G. Stroke at the university of port Harcourt teaching hospital, rivers state, Nigeria. Trop Doct. 2009;39(3):150–2.
11. Sagui E, Saliou PM, Dubecq C, Khadi BF, Niang A, Gning S, Jean-Pierre B, Sane M, Debonne JM. Ischemic and hemorrhagic strokes in Dakar, Senegal. A hospital based study. Stroke. 2005;36(9):1844–7.
12. Williams C, Shephard T. A brief descriptive analysis of stroke features in Virginia. Neuroepidemiology. 2003;22(1):31–6.
13. Ojemann R, Heros R. Spontaneous brain hemorrhage. Stroke. 1983;14:468.
14. Kwarisiima L, Mukisa R, Nakibuuka J, Matovu S, Katabira E. Thirty-day stroke mortality and associated clinical and laboratory factors among adult stroke patients admitted at Mulago Hospital, Uganda. AJNS.2014;33(1):79–86.
15. Ogun SA, Oluwole O, Ogunseyinde AO, Fatade B, Odusote KA. Misdiagnosis of stroke – a computerized tomography scans study. West Afr J Med. 2000;19(1):19–22.
16. Nyame PK, Jumah KB, Adjei S. Computerised tomography scan of the head in the evaluation of stroke in Ghanaians. East Afr Med J. 1998;75:17–9.
17. Adams GF, Hurwitz LJ. Cerebrovascular disability in the aging brain. Edinburgh/London: Churchill Livingstone; 1974.
18. Adams GF, Hurwitz LJ. Mental barriers to recovery from strokes. Lancet. 1963;2(7307): 533–7.
19. Connor MD, Walker R, Modi G, Warlow CP. Burden of stroke in black populations in sub-Saharan Africa. Lancet Neurol. 2007;6:269–78.
20. Garbusinski JM, van der Sande MA, Bartholome EJ, et al. Stroke presentation and outcome in developing countries: a prospective study in the Gambia. Stroke. 2005;36:1388–93.

Chapter 9
Challenges of Diagnosis and Treatment of Epilepsy at Mulago National Referral Hospital in Kampala, Uganda

Edward Ddumba

Abstract Epilepsy is a common condition in Low Income Countries like Uganda. These countries are overburdened by infectious diseases like Malaria, Tuberculosis and HIV/AIDS. Uganda is going through an epidemiologic transition from communicable diseases to non-communicable diseases including epilepsy. The country has not put in place strategies to address the new realities of the increasing burden of non-communicable diseases like diabetes, hypertension and epilepsy. There are tremendous challenges in terms of infrastructure, human resources for health, diagnostics and medical supplies for effective treatment of these conditions. Many communicable and non-communicable diseases may present with symptomatic seizures which are often mistaken for *epilepsy the disease.* This article discusses the challenges health workers meet in diagnosing, investigating and treating epilepsy in a limited resource setting at Mulago National Referral Hospital in Kampala, Uganda.

Keywords Epilepsy • Diagnosis • Low income countries • Limited resource setting • Challenges

Introduction

Health Statistics

Uganda lies in East Africa and has no direct access to the sea except through Kenya and Tanzania. It has an estimated population of 33 million people (UBOS 2012). More than 50 % of the population is below 15 years of age. Life expectancy is estimated to be 50.4 years. The HIV/AIDS prevalence rate has risen to 7.2 % in the last 2 years after it had dropped to 6.4 %. There are 1.2 million Ugandans living with HIV/AIDS.

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S. Musisi, S. Jacobson (eds.), *Brain Degeneration and Dementia in Sub-Saharan Africa*, DOI 10.1007/978-1-4939-2456-1_9

Table 9.1 Health statistics for Uganda

Health statistic	Estimate
Life expectancy	50.4 years
Maternal mortality ratio	438 per 100,000
Population per doctor	18,700
Population per nurse	3,065
Health service accessibility at <5 km	49 %
Per capita expenditure on health	12US$
Per capita expenditure on drugs	3US$

Over 30 % of the population lives below the poverty line and more than 70 % of the population is rural. Uganda has a GDP growth rate of 6 % per annum. The adult literacy rate is 66.8 %. Table 9.1 summarizes the statistics.

Organization of Health Services in Uganda

The health services are organized in order of size and complexity of services offered organized as from Health Centers: I (village) II (parish), III (Sub-county), IV (County) to District General Hospitals, then Regional Referral Hospitals and finally National Referral Hospitals at the top. There are two National Referral Hospitals namely, Mulago National Referral General Hospital and Butabika National Referral Mental Hospital. The latter hospital is a specialist facility for psychiatry disorders. Mulago Hospital is the main hospital for all other general medical conditions. It is also the teaching hospital for Makerere University College of Health Sciences as Butabika is also a Makerere University teaching hospital for mental disorders. Mulago hospital has a bed capacity of 1,500 beds and receives approximately 2,000 out patients per day. The Department of Internal Medicine is one of the bigger Departments and offers Neurology services for both in patients and out patients. The Neurology Clinic runs every week on Wednesdays. It is staffed by Physicians, Medical Officers and Nurses. It has EEG services and neuro-imaging with a one 16 slice CT scanner. On average, the Neurology clinic attends to 30 patients per day of which 6–0 patients will present with a seizure disorder (Ref). Some of the patients are referred from other health facilities but the majority of the patients are self referrals or follow-up patients who have been discharged from the inpatient wards. The main stay of a diagnosis of epilepsy is based on a thorough record of the patient's signs and symptoms followed by a carefully done clinical assessment of the patient with particular emphasis on the Nervous System. The history is collaborated by a reliable eye witness account of the event(s) or clinical observation of a seizure by a health worker. Wherever possible, EEG, brain CT scan, blood counts, Hb-electrophoresis, blood slide for malaria parasites, renal function tests, blood

sugar, VDRL and HIV serology are requested for. The drugs available at the Mulago neurology clinic include: Phenytoin, Carbamezapine, Sodium valproate, Phenobarbitone, Clonazepam and Ethosuximide. There are no neurology clinics in other hospitals. The neurologist per population ratio is 1:7,000,000 if we include the two paediatric neurologists. Most of the seizures are secondary to cerebrovascular disease, CNS infections or head trauma from road traffic accidents or birth injury.

Epidemiologic Transition

Like other developing countries, Uganda has been grappling with the burden of infectious diseases including, malaria, HIV/AIDS, Tuberculosis and Malnutrition. In the last decade, the prevalence of non-communicable diseases has increased partly due to the adaption western life styles especially the use of fast foods and beverages. The population is also living longer with those over 60 years increasing. This predisposes to hypertension, stroke and age-related degenerative brain diseases with all their complications including seizure disorders.

Epilepsy: Definition and Classification

Seizures are the hallmark of epilepsy. An epileptic seizure is a transient occurrence of signs and or symptoms due to abnormal and excessive neuronal activity in the brain [3]. Epilepsy is characterized by at least one seizure, an enduring predisposition to recurrent epileptic seizures and associated cognitive, psychological and social sequelae. The classification of epilepsy as follows:

A. Partial Seizures (Focal seizures)

- Simple partial seizures: These can be motor, sensory, autonomic or psychic and do not alter consciousness
- Complex partial seizures with impairment of consciousness
- Simple partial or complex partial with secondary generalization

B. Primary generalized seizures

- Absence seizures: typical and atypical
- Myoclonic seizures
- Clonic seizures
- Tonic seizures
- Tonic-clonic seizures
- Atonic seizures

C. Unclassified because of incomplete data

Challenges in Epilepsy Management in Uganda

The diagnosis and subsequent treatment of epilepsy poses several challenges in a resource limited setting as obtains at Mulago Hospital and in Uganda and Africa at large. The following is an elaboration on some of these challenges as they apply in Uganda.

Challenge 1: Epilepsy Is Common

Although epilepsy is common in Uganda, there is no accurate data to guide the process of diagnosis. However it is the most common neurological disorder in both children and adults.

The factors that are responsible for the high prevalence of epilepsy in Uganda include:

- High prevalence of cerebral malaria and CNS infections e.g. meningitis and encephalitis
- Perinatal causes including birth trauma from poor obstetric care.
- Head trauma from road traffic accidents especially boda – boda motor cycle accidents
- Cerebrovascular disease including ischemic and hemorrhagic strokes
- Brain tumors
- Arterial-venous malformations
- HIV/AIDS and its opportunistic CNS infections: Cryptococcal meningitis and Toxoplasmosis
- Parasitic infections like neurocystercercosis
- Neurosyphylis
- Alcohol and substance abuse as well as other brain toxins
- Degenerative diseases of the brain including multi-infarct (vascular) dementia, pre senile and senile dementias such as Alzheimer's disease, Parkinsonian dementia, Fronto-temporal dementia etc.

Challenge 2: Epilepsy Diagnosis Carries Stigma

- Most of the Ugandan population still thinks that epilepsy is caused by witch craft, evil spirits or is infectious.
- A large proportion of the population believe that western type of medicines do not cure this disease hence many would seek the services of a traditional healers before coming to the hospital and even afterwards.
- Many families keep the patient at home for fear of bringing shame to the family.

Challenge 3: Difficulty in Differentiating Epilepsy from Non-epilepsy Disorders

Misdiagnosis of epilepsy is common even in even in more advanced centers that care for epilepsy patients. This problem may explain none response to anti-epilepsy drugs that has been observed in presumed epilepsy patients (Chadwick and Smith 2002). Many patients who are misdiagnosed as epileptic have an EEG recording that has been misread and therefore misinterpreted as epileptiform. Many clinicians still equate an abnormal EEG recording to proof that epilepsy exists and are likely to conclude that a negative EEG excludes the diagnosis of epilepsy. Below are some of the conditions that are often misdiagnosed as epilepsy in the Uganda situation. The problem is made worse by lack of more advanced diagnostic facilities like EEG – video monitoring.

Some of the Conditions Misdiagnosed as Epilepsy in Uganda

- Psychogenic Non-Epilepsy Seizures (PNES)
- Syncopal attacks
- Transient ischemic attacks
- Cardiac dysrhythmias
- Sleep disorders e.g. night terrors
- Cataplexy
- Sleep starts
- Psychiatric disorders
- Transient global amnesia
- Episodic Dizziness and vertigo
- Hemifacial spasm
- Non epileptic Myoclonus
- Acute dystonic reactions secondary to the use of neuroleptics
- Complicated migraine
- Twilight or fugue states
- Panic attacks
- Hypoglycemia especially in diabetics on medication
- Benign non specific symptoms misinterpreted as seizures

Challenge 4: Limited Epilepsy Services

- There are no trained Epilepsy specialists in Uganda. Neurologists are only a handful.
- There are no facilities to train epilepsy specialists in Uganda
- There is inadequate exposure of medical students to the basics of epilepsy and neurology

- There are scarce imaging facilities and EEGs in the country
- The supply of antiepilepsy drugs is inadequate and erratic

Challenge 5: Lack of Reliable Data

- No epilepsy prevalence and incidence studies have been done in Uganda
- No large community based studies have been done to guide the planning process for the provision of epilepsy services
- We don't know the epilepsy burden in Uganda and the factors responsible for this silent epidemic
- Some diseases have been branded epileptic without adequate epidemiological and clinical data and causes have been attributed to them e.g. Nodding Syndrome and O. volvulus.

Opportunities on the Horizon

The epidemiologic transition from communicable to non-communicable diseases has been recognized by the Uganda Ministry of Health and Development Partners. There has also been started a more integration of Neurology in the Medical School curriculum and there are promising collaborations with Universities abroad.

Conclusion

Epilepsy is a common condition in Uganda but under diagnosed and also often misdiagnosed. Most of the epilepsy cases are symptomatic of underlying brain disorder. Infective and traumatic causes are common. The prevalence of degenerative diseases of the brain is increasing and contributing to symptomatic epileptic seizures. There is an urgent need to carry out population surveys to establish the prevalence and incidence of epilepsy in Uganda and to address the causes for the many symptomatic epileptic seizures.

References

1. Uganda Health and Demographic Survey 2011.
2. Mulago Hospital Records 1994–2007.
3. Fisher RS, van Emde Boas W, Blume W, et al. Epileptic seizures and epilepsy definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia. 2005;46(4):470–2.

Chapter 10
Psychiatric Aspects of HIV Infection in Sub-Saharan Africa

Etheldreda Nakimuli-Mpungu

Abstract Psychiatric assessment should always be incorporated into any assessment of patients with HIV/AIDS. To begin the process of HIV care, routine HIV testing coupled with pre- and post-test counseling should be offered to patients accessing outpatient and inpatient mental health services. Referral networks to other healthcare facilities should be put in place so that medical assessments to rule out organic causes can be treated. Mental health care providers should be equipped with skills and tools to provide prevention interventions for persons living with mental disorder and HIV/AIDS. Likewise, HIV healthcare personnel need to be equipped with skills and tools to be able to carry out routine mental health assessments/screening for the common mental health problems in HIV/AIDS.

Lastly, HIV infection causes significant brain degeneration with resultant affective (depression, mania), psychotic, anxiety and cognitive disorders, the latter commonly referred to as HIV-Associated neurocognitive disorders or HAND. These neuropsychiatric disorders occur in both children and adults. Untreated, they will compromise adherence to treatment initiatives and pose significant HIV-infection risk behavior. All this calls for integration of mental health care in any HIV-care program for their early detection and treatment for better outcomes and improved quality of life for PLWHA and for prevention strategies if we are to stem the epidemic.

Keywords HIV depression • HIV related secondary mania • Severe mental illness • People living with HIV AIDS (PLWHA) • Bipolar disorder co-morbid with HIV/AIDS

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S. Musisi, S. Jacobson (eds.), *Brain Degeneration and Dementia in Sub-Saharan Africa*, DOI 10.1007/978-1-4939-2456-1_10

Introduction

Psychiatric disorders have been reported among people at risk for or infected by HIV worldwide. Addressing co-occurring psychiatric disorders is a necessary step in control of the HIV epidemic [1, 2]. The psychiatric sequelae of HIV infection have etiologies that involve biological, psychological and social factors. These include the natural and expected grief response to being diagnosed with a terminal illness, later reactions to disability and illness as well as exacerbation of pre-existing psychiatric illness. On the other hand new psychiatric symptoms and syndromes may occur as a result of direct effect of the HIV virus on the brain, or as a consequence of HIV-related opportunistic diseases and as side effects of HIV-related treatments. Despite the impressive reduction of HIV-related morbidity and mortality where antiretroviral therapy (ART) is available, reports of psychiatric repercussions of HIV disease are on the increase [3].

The consequences of untreated psychiatric disorders among those with HIV infection include reduced coping capacity at the time of HIV diagnosis, poor HIV-related disease prognosis, failure to access HIV care and treatment, erratic adherence to antiretroviral regimens, diminished quality of life, greater social burden, increased health-care costs and higher mortality [4–7]. Among persons living with HIV, there is a documented mental health treatment gap that needs to be addressed. This gap is large for both severe and common mental disorders worldwide [2], but more pronounced sub-Saharan Africa.

Understanding psychiatric disorders among people living with HIV and AIDS (PLWHA) in sub-Saharan Africa can help better define priorities and needed resources to reduce the incidence, the prevalence and the burden of HIV disease on individuals with these disorders and on the communities in which they receive care. In this chapter we review published epidemiology of mental disorders among PLWHA in sub-Saharan Africa. We begin with the most described HIV related-psychiatric disorders among people with HIV: depression; mania; anxiety (including PTSD); and psychosis. We also discuss sero-prevalence of HIV and risk behaviors in individuals with severe mental illness (SMI) as well as the impact of SMI on HIV treatment outcomes in sub-Saharan Africa.

Depression

A systematic review of the literature on HIV and mental illness in developing countries performed by Collins et al. (2006) found 13 studies published between 1990 and 2005 from middle or low-income countries that reported rates of psychiatric disorder based on diagnostic interviews or psychiatric symptom scales [8]. Rates of depression ranged from 0 % to 63.3 % among HIV-positive participants. In the largest of these studies, investigators recruited every third subject seeking medical services in Bangkok, Thailand; Kinshasa, Democratic Republic of Congo; Nairobi,

Kenya; Sao Paolo, Brazil and Munich, Germany [9]. To ascertain psychiatric diagnoses, the Composite International Diagnostic Interview (CIDI), a structured diagnostic interview developed by the WHO and validated for cross-cultural use, was used and to ascertain depressive symptoms the Montgomery-Asberg Depression Rating Scale (MADRS) was used. Rates of depression among asymptomatic HIV-positive people in the four developing country sites averaged 6.0 % (range: 0 % in Kinshasa to 10.9 % in Sao Paolo). Symptomatic HIV-positive patients had rates of depression, ranging from 4.4 % in Kinshasa to 19.6 % in Sao Paolo. Depression was the only diagnosis for which a higher prevalence among symptomatic HIV-positive patients reached significance compared with HIV-negative controls.

Since 2005, the expansion of ART programs with scaling up of ART provision in rural areas in Sub-Saharan Africa has led to more research on depression of HIV positive individuals. These studies are summarized in Table 10.1. In 30 studies, HIV positive individuals using ART have been screened with various depression screeners resulting in prevalence estimates of significant depression symptoms ranging from 9.4 % [10] to 81 % [11]. Six studies report on prevalence rates of current major depression ranging from 11.8 % [12] to 34.9 % [13]. Two studies report on prevalence rates of lifetime major depression ranging from 13.3 % [14] to 18.1 % [13] among HIV positive individuals. The Ugandan studies estimate prevalence rates of significant depression symptoms to range from 30 % [15] to 54 % [16].

The studies on prevalence of depression in HIV positive populations give variable prevalence estimates of depression; from as high as 81 % in HIV positive individuals attending an HIV treatment program in Rwanda to as low as 0 % in HIV positive individuals in the Democratic Republic of Congo (DRC). If the findings of these studies are to be taken at face value, then eight of ten HIV positive patients in Rwanda has significant depression symptoms and depression is non-existent in DRC. A critical re-evaluation of these studies is required given the variability of findings.

A recent systematic review of studies documenting the prevalence of significant depressive symptoms and major depression among HIV-positive individuals enrolled in ART programs in sub-Saharan Africa, found prevalence estimates of 31 % and 18 %, respectively [17]. These estimates are much higher than prevalence estimates of depressive symptoms and major depression in community studies in Uganda and South Africa [2], suggesting an increased risk of depressive symptoms and major depression in HIV-positive individuals.

Most studies reporting on the prevalence of depression among PLWHA, have not assessed subjects for bipolar disorder [18], an important diagnosis to rule out. Many studies screened or assessed people for depressive symptoms and without further evaluation, no distinction can be made between subclinical depression and other depressive disorders besides major depression [15, 19, 20]. The few studies that have evaluated study participants with a diagnostic interview have neither reported on subclinical depression nor lifetime depressive disorders [13, 21, 22]. Knowledge of the prevalence of specific depressive disorders would allow for better resource allocation to provide required treatments (e.g., pharmacotherapy and psychotherapies) [23, 24] while management of lifetime depression would focus on relapse prevention using psychosocial interventions and maintenance medication.

Table 10.1 Summary of studies describing prevalence estimates of depression symptoms and major depression among HIV positive individuals and their impact on adherence to ART in sub-Saharan Africa

Author	Location Study design Setting Sample size % Females	Measures of depression symptoms Validation measure % depression symptoms	Measure of major depression % major depression	Association between depression and ART adherence
Adewuya 2008†‡	Nigeria Cross-sectional HIV psychosocial support center N = 87 56.3 % females	15.1 % depression symptoms	Mini international neuropsychiatric interview NA 11.8 % major depression	NA
Adewuya 2010†§	Nigeria Cross-sectional HIV psychosocial support center N = 182 53 % females	General health questionnaire (12 items) Cut-off score : ≥ 3 Not locally validated in study population 65.4 % depression symptoms		Depressed patients were less likely to be adherent to ART compared to non-depressed patients AOR = 0.23; 95% CI (0.09–0.55)
Amberbir 2008†§	Ethiopia Longitudinal HIV treatment clinic attached to general hospital Baseline N = 400 59.8 % females	Becks depression Inventory (21 items) Cut-off score: ≥10 Not locally validated in study population 55.8 % baseline depression symptoms		Depressed patients were less likely to be adherent to ART compared to non depressed patients OR = 0.47; 95% CI (0.26–0.90) Association between alcohol use and adherence was not assessed
Byakika-Tusime 2009§	Uganda Cross-sectional Mother-to-child-transmission plus program N = 177 70.1 % females	Becks Depression Inventory (BDI) (21 items) Cut-off score : not reported Not locally validated in study population Mean BDI score for the sample was 9.74 (SD = 4.6)		Among those who had used ART for less than 6 months, the odds of adherence decreased by 99 % for every unit increase in depression symptom score AOR = 0.01; 95% CI (0.00–0.77) Among those "stable" on ART, the odds of adherence decreased by 61 % for every unit increase in depression symptom score AOR = 0.39; 95% CI (0.11–1.34)

(continued)

Table 10.1 (continued)

Author	Location Study design Setting Sample size % Females	Measures of depression symptoms Validation measure % depression symptoms	Measure of major depression % major depression	Association between depression and ART adherence
Cohen 2009†	Rwanda Cross-sectional HIV psychosocial support center N = 658 100 % females	Center for epidemiological studies depression scale (20 items) Cut-off score: ≥16 Not locally validated in study population 81 % depression symptoms		NA
Do 2010†	Botswana Cross-sectional HIV treatment clinic attached to general hospital N = 300 76.3 % females	Becks depression inventory (21 items) Cut-off score: ≥14 Not locally validated in study population 28.3 % depression symptoms		NA
Etienne 2010§	Kenya, Uganda, Zambia, Nigeria, and Rwanda Cross-sectional HIV treatment clinics attached to general hospitals N = 921 65.4 % females	Factor scores of depression were constructed from three questions of depression (persistent feelings of sadness/ hopefulness in the past month, frequency of crying in the past month, and frequency of feeling confused in the past month) Reliability score 0.67 57.2 % low depression scores, 22.0 % medium depression scores, 20.8 % high depression scores		Those with high depression scores were less likely to adhere to ART compared to those with low scores AOR = 0.57; 95% CI (0.39–0.84) Those who never used alcohol were more likely to be adherent to ART than those who used alcohol AOR = 2.14; 95% CI (1.36–3.37)

(continued)

Table 10.1 (continued)

Author	Location Study design Setting Sample size % Females	Measures of depression symptoms Validation measure % depression symptoms	Measure of major depression % major depression	Association between depression and ART adherence
Farley 2010†§	Nigeria Cross-sectional HIV treatment clinic attached to a general hospital N = 399 70 % females	Center for epidemiological studies depression scale (20 items) Cut-off score: ≥21 The Cronbach alpha: 0.86 13 % depression symptoms		Study participants with CES-D scores ≥16 were less likely to be adherent to ART compared to those with scores < 16 OR = 0.23; 95% CI (0.08–0.68) No association between AUDIT scores and pharmacy refill rate OR = 1.55; 95% CI (0.19–12.46)
Kagee 2010†	South Africa Cross-sectional HIV clinics within primary health care facilities N = 85 75.3 % females	The Beck Depression Inventory 1(BDI-1) Cut-off score : ≥18 Cronbach's alpha: 0.85 37.6 % depression symptoms		NA
Kaharuza 2006†	Uganda Cross-sectional HIV psychosocial support center N = 1,017 77 % females	A modified center for epidemiological studies depression scale (12 items) was computed by removing the CES-D items reflecting somatic complaints Cut-off score: ≥23 Cronbach's alpha: 0.85 47 % depression symptoms		NA

(continued)

Table 10.1 (continued)

Author	Location Study design Setting Sample size % Females	Measures of depression symptoms Validation measure % depression symptoms	Measure of major depression % major depression	Association between depression and ART adherence
Kekwaletswe 2011#§†	South Africa Cross-sectional HIV treatment center N = 304 68 % females	Center for Epidemiological studies Depression scale (20 items) Cut-off score : ≥16 Cronbach's alpha: 0.92 59.2 % depression symptoms		Patients with CES-D score of >16 were less likely to be adherent to ART compared to those with scores < 16 OR = 0.43;.95 % CI (0.25–0.72) Patients with AUDIT score >8 were less likely to be adherent to ART compared to those with scores <8 OR = 0.30; 95 % CI (0.19–0.73)
Lawler 2010†‡	Botswana Cross-sectional HIV treatment clinic attached to a general hospital N = 120 50 % females	Beck Depression Inventory-Fast Screen (BDI-FS) Cut-off score: ≥4 Cronbach's alpha: 0.84 38 % depression symptoms	Prime-MD Mood Module (MM) 24 % major depression	NA
Martinez 2008†	Uganda Cross-sectional HIV treatment clinic attached to a general hospital N = 421 63.2 % females	A modified depression section of the Hopkins Symptoms checklist with somatic measures removed. Cut-off score: ≥1.75 Cronbach's alpha: 0.74 18.8 % depression symptoms		NA
Marwick 2010‡	Tanzania Cross-sectional HIV treatment clinic attached to a general hospital N = 220 74 % females	Clinic interview schedule –Revised Previously validated in primary health clinic attendees Cronbach's alpha for this sample not reported	15.5 % major depression	NA

(continued)

Table 10.1 (continued)

Author	Location Study design Setting Sample size % Females	Measures of depression symptoms Validation measure % depression symptoms	Measure of major depression % major depression	Association between depression and ART adherence
Monahan 2009†	Kenya Cross-sectional HIV psychosocial support center N = 347 73 % females	Patient health questionnaire (9 items) Cut-off score: ≥10 Cronbach's alpha 0.78 34 % depression symptoms		NA
Myer 2008†‡	South Africa Cross-sectional Primary health care facility N = 465 75 % females	Center for Epidemiological studies Depression scale Cut-off score : ≥ 6 45 % depression symptoms. Locally validated in study population. Sensitivity: 79 % Specificity: 61 %	Mini international neuropsychiatric interview 14 % major depression	NA
Nachega 2011#†	South Africa. Longitudinal HIV treatment center Baseline N = 274 60 % females	Brief Symptom Inventory (BSI) 51 items Cut-off score: ≥9 Not locally validated in study population 25.4 % baseline depression symptoms		Depression scores were not associated with ART adherence at 12 and 24 month follow-up. OR =0.5, 95% CI (0.15–1.56) Alcohol abuse was a baseline independent predictor of ART adherence OR 2.4, 95% CI (1.20–5.0)
Nakasujj 2010†	Uganda Longitudinal HIV treatment clinic attached to a general hospital N = 102 (baseline) 72.6 % females	Center for epidemiological studies depression scale (20 items) Cut-off score: ≥16 Not locally validated in study population 54 % baseline depression symptoms		NA

(continued)

Table 10.1 (continued)

Author	Location Study design Setting Sample size % Females	Measures of depression symptoms Validation measure % depression symptoms	Measure of major depression % major depression	Association between depression and ART adherence
Nakimuli-Mpungu 2009†§	Uganda Cross-sectional HIV treatment clinic attached to a Mental hospital N = 122 78.% females	Self-reporting questionnaire (20 items) Cut-off score: ≥6 Not locally validated in study population 30.3 % depression symptoms		Those with significant depression symptoms were less likely to adhere to ART compared to those without significant depression symptoms AOR = 0.27; 95% CI (0.10–0.72)
Nakimuli-Mpungu 2010†	Uganda Cross-sectional HIV treatment clinic attached to a general hospital N = 244 63.9.% females	DSM-IV symptom checklist Cut-off score: ≥6 Not locally validated in study population 40 % depression symptoms		NA
Olley 2006‡	South Africa Longitudinal HIV treatment clinic attached to a general hospital N = 149 (baseline) 70.5.% females		Mini international neuropsychiatric interview Not locally validated in study population 34.9 % major depression	
Patel 2009	Zimbabwe Cross-sectional HIV treatment clinic attached to a general hospital N = 200 100 % females	Shona symptom questionnaire (14 items) Cut-off score : not reported Cronbach's alpha 0.86 Mean depression score 28.44 (9.28)		NA

(continued)

Table 10.1 (continued)

Author	Location Study design Setting Sample size % Females	Measures of depression symptoms Validation measure % depression symptoms	Measure of major depression % major depression	Association between depression and ART adherence
Pearson 2009†	Mozambique Longitudinal HIV treatment clinic N = 277 (baseline) 56.3 % female	Center for epidemiological studies depression scale (10 items) Cut-off score: ≥10 Cronbach's alpha: 0.74 9.4 % baseline depression symptoms		NA
Peltzer 2010§	South Africa Cross-sectional District hospital N = 519 73.4 % females	Center for epidemiological studies depression scale (10 items) Cut-off score: not reported Cronbach's alpha: 0.54 NA		The odds of adherence decreased by 29 % for every unit increase in depression symptom score OR = 0.88; 95% CI (0.80–0.96)
Pourpad 2007†	Senegal Cross-sectional HIV treatment clinic N = 200 63.5 % females	Center for epidemiological studies depression scale (20 items) Cut-off score : ≥16 Not locally validated in study population 18 % depression symptoms		NA
Ramadhani 2007†§	Tanzania Cross-sectional HIV treatment clinic N = 150 63 % females	Hopkins symptom checklist (25 items) Cut-off score: ≥1.75 Cronbach's alpha: 0.93 21 % depression symptoms		Those with significant depression symptoms were less likely to adhere to ART compared to those without significant depression symptoms AOR = 0.48; 95% CI (0.15–1.56)

(continued)

Table 10.1 (continued)

Author	Location Study design Setting Sample size % Females	Measures of depression symptoms Validation measure % depression symptoms	Measure of major depression % major depression	Association between depression and ART adherence
Simbayi 2007†	South Africa Cross-sectional Psychosocial support center N = 1,063 60.5 % females	Modified center for epidemiological studies depression scale (11 items) Cut-off score: ≥16 Cronbach's alpha: 0.93 30 % depression symptoms		NA
Spies 2009‡	South Africa Cross-sectional Primary health care HIV treatment facilities N = 429 76 % females	Kessler-10 Cut-off score: ≥28 Cronbach's alpha: 0.87	Mini international neuropsychiatric interview 13 % major depression	NA
Wagner 2011†	Uganda Cross-sectional HIV treatment clinic attached to a general hospital N = 602 68 % females	Patient health questionnaire (9 items) Cut-off score: ≥10 The Cronbach alpha coefficient for the sample not reported 13 % depression symptoms		NA
Weidle 2006†	Uganda Longitudinal Psychosocial support center N = 987 74 % females	Modified center for epidemiological studies depression scale (20 items) Cut-off score: ≥23 Cronbach's alpha not reported 45 % baseline depression symptoms		NA

[#] This study was published as an abstract
[†] These studies reported prevalence rates of depression symptoms
[§] These studies reported the association between depression symptoms and adherence to ART
[‡] These studies reported prevalence rates of major depression

In Uganda, a recent cross-sectional study of HIV positive individuals in a rural ART program in the southern regions of the country found the prevalence estimates of any depressive disorder, subclinical depression, both current and lifetime major depression, and bipolar depression were 46.4 %, 17.8 %, 25 % and 3.6 % respectively [25]. In comparison to non-depressed patients, those with sub-clinical depression were less likely to have high levels of self-efficacy, more likely to be using ART for less than 1 year, had advanced HIV disease and current alcohol use disorders (AUD's). Those with both current and lifetime depressive disorders were less likely to be 85 % adherent to antiretroviral therapy (ART), have social support and high levels of self-efficacy, more likely to have tuberculosis and past manic episodes. Those with only lifetime depressive disorders were more likely to have current alcohol use disorder (AUD) and past manic episodes. The large proportion of HIV positive individuals with depressive disorders or significant depressive symptoms in ART programs in Uganda and other developing countries who remain undiagnosed and untreated is indeed a major unmet healthcare need.

Depression and Non-adherence to ART

In 2005, two African studies investigated the association between current significant depression symptoms and adherence to ART. In both studies, the association did not attain statistical significance. Since then, two Ugandan studies, [15, 26]; one study from South Africa [27] Nigeria [28] and Ethiopia [29] have investigated this association. All studies report a statistically significant association between current significant depression symptoms and poor adherence to ART. Qualitative studies in sub-Saharan Africa on barriers to ART adherence echo similar findings [30–32].

Given that depression is a recurrent complex mood disorder with various DSM-5 categories, it is important to investigate the relationship between lifetime depressive disorders and adherence to ART. A recent case-control study among rural HIV positive individuals using anti-retroviral therapy revealed that HIV positive individuals with lifetime depressive disorders had an increased risk of non-adherence to ART after controlling for education status, income, self-efficacy, perceived social support, cognitive impairment and current alcohol use disorders [32]. This association was stronger in females than males. This finding indicates that it would be important to closely monitor and support individuals with a history of lifetime depressive disorders who are initiating ART.

Studies have shown that untreated depressive disorders increase HIV transmission risk behaviors [33, 34], decrease immune status [35, 36] and decrease adherence to antiretroviral therapy (ART) [37–40] which may result in decreased clinical effectiveness and potential development of drug resistance [41, 42]. Thus, depression does pose challenging barriers to effective medical care at multiple points along the continuum of HIV medical care engagement and treatment (i.e. the 'HIV treatment cascade') [43]. Untreated depression has been associated with a lower likelihood of receiving anti-retroviral drugs [44, 45], poor adherence [34, 46] and

increased morbidity [47–50] and mortality [35]. Depression is a predictor of clinical progression independently of non-adherence behaviors [49]. Depression is frequently under diagnosed and when recognized is often poorly treated, particularly in primary medical settings where most HIV/AIDS patients receive care [7, 51]. Mounting evidence suggests that effective treatment of depression in HIV patients may have benefits for their HIV-treatment retention, ART adherence, and virologic suppression, and, therefore, for community viral load [43].

HIV-Related Secondary Mania

Mania in a patient with HIV/AIDS may occur as a phase of a coexisting bipolar disorder, or it may be secondary to the direct neuronal effects of HIV infection [4, 52], treatments for HIV infection [53–55], or HIV-related secondary infections of the brain [56]. Affected patients appear to present with severe psychopathology [57, 58]. In developed countries, prevalence studies have shown that mania secondary to HIV infection is common [59, 60], and it occurs more among individuals with AIDS than among those with HIV infection alone [57, 60]. Researchers have previously hypothesized that mania occurring in the early stages of HIV infection may represent bipolar disorder in its manic phase, whereas mania in persons with AIDS is secondary mania linked to the pathophysiology of HIV brain infection [59, 61].

The evidence for an etiological association with HIV neuropathy was bolstered by a prospective study of HIV-positive patients with and without mania that demonstrated a protective effect from an antiretroviral agent able to penetrate the central nervous system [62]. However, given the small sample sizes used in these studies, any conclusions drawn from them should be considered tentative. The epidemiology of mania secondary to HIV infection in Uganda and other African countries that have high rates of HIV infection and limited access to highly active antiretroviral therapy remains largely unknown.

A study in Uganda compared the presentation and correlates of primary mania in HIV-negative patients with those of first episode secondary mania in HIV-positive patients [63]. The majority of HIV-positive patients with mania met criteria for first-episode secondary mania. Compared with HIV-negative patients with primary mania, they were predominantly female, age 30–49 years and of low socioeconomic and educational status. A significant number were divorced or had been widowed as a result of losing spouses to AIDS. Clinically, the majority presented in late stages of HIV infection, in WHO clinical stages 3 and 4. They were irritable and had aggressive and disruptive behaviors, decreased need for sleep, over talkativeness, and high rates of cognitive impairment, paranoid delusions, visual hallucinations, and auditory hallucinations as well as high rates of HIV-related signs and symptoms [63].

These findings show that first-episode secondary mania in HIV-positive individuals and primary mania in HIV-negative individuals are clinically and immunologically distinct. The relationship between secondary mania and depressed CD4 counts suggests that in the setting of an AIDS epidemic in poor countries where the costs

of measures of immune status, such as CD4 cell counts, are prohibitive, secondary mania maybe used as an indicator to initiate highly active antiretroviral therapy [63]. Knowledge about the presentation of secondary mania in HIV infection may improve its clinical recognition and hence guide the development of early, effective interventions to control symptoms that not only interfere with a patient's ability to adhere to treatment but also predispose patients to HIV risk behaviors, which may lead to further spread of HIV infection.

Early Onset Versus Late Onset HIV-Related Secondary Mania

A follow –up study compared the demographic and clinical characteristics of HIV-positive patients with early-onset and late-onset first-episode secondary mania in HIV infection, in order to determine whether baseline characteristics might provide insights into appropriate methods of assessment and management [61]. This study showed that among HIV-positive patients who met criteria for secondary mania, patients with early-onset and late-onset mania had comparable socio-demographic characteristics. Clinically, consistent with previous findings [57], patients with late-onset secondary mania had more manic symptoms on the Young Mania Rating Scale, YMRS. They were more irritable and had a more decreased need for sleep than patients with early-onset secondary mania.

Bipolar Disorder Co-morbid with HIV/AIDS

Another study in Uganda revealed that patients with bipolar mania, regardless of HIV status, had a more-or-less similar demographic profile. They had comparable age at onset of first affective symptoms, marital and education status. Generally, these findings are in keeping with previous descriptions of demographic characteristics of patients with bipolar disorder elsewhere [64]. It is interesting to note that, at the time of assessment, HIV-positive patients with bipolar disorder were older than the HIV-negative patients. This indicates that the HIV-positive patients had a longer duration of bipolar illness than the HIV-negative patients. One possible explanation for this finding could be that the lack of routine screening for HIV infection in our psychiatric hospital may have delayed diagnosis of HIV in the majority of these patients. Previous researchers have argued that HIV-positive patients with various bipolar subtypes may have associated impulsive, risk-taking traits that may play a role in HIV risk-behavior such as unprotected sex [65].

This study also confirmed the hypothesis that the demographic profiles of HIV-positive patients with bipolar mania and those with secondary mania were different. Although, at assessment, both groups had comparable ages, those with primary bipolar mania were younger when they had their first episode of affective symptoms. Also, the bipolar-mania group had more education and was more likely to be

employed than the secondary-mania group. However, both groups of HIV-positive patients had comparable female-to-male ratios, with women being more often affected than men. In Africa, where heterosexual transmission predominates, men usually have multiple sexual partners. Therefore women are more at risk of acquiring HIV infection [66].

Clinically, as expected, the HIV-positive patients, regardless of mania status, had more immune suppression, more cognitive impairment, and more severe manic symptoms, with more irritability and more psychotic symptoms than the HIV negative patients with bipolar mania.

Interestingly, this study also shows that the HIV-positive individuals regardless of manic status had comparable severity of manic symptoms. This finding suggests that the presence of HIV infection in patients with bipolar disorder may alter subsequent manic episodes, making them similar to that of HIV-positive patients with secondary mania. Therefore, one may argue that recurrent manic episodes in patients with bipolar disorder infected with HIV may be related to the pathophysiology of HIV infection in the brain.

We also observed that the HIV-positive patients with bipolar mania had more cognitive impairment, more immune suppression, and, hence, more HIV-related illnesses than those with secondary mania. This finding is in contrast to previous findings from earlier reports, which found that HIV-positive patients with secondary mania have more cognitive impairment and more immune suppression than HIV-positive patients considered to have bipolar mania [57]. Possible explanations could be that patients with bipolar disorder are already cognitively and functionally impaired by their illness by the time they acquire HIV infection. A growing body of evidence suggests that bipolar patients exhibit neuropsychological impairment that persists even during the euthymic state, which may be a contributory factor to poor psychosocial outcome [67].

Anxiety Disorders

Anxiety is a common symptom in HIV-infected patients. When anxiety symptoms are severe or persistent to the extent that they interfere with normal functioning, the affected patient may have an anxiety disorder. These disorders include panic disorder, generalized anxiety disorder, obsessive-compulsive disorder, and post-traumatic stress disorder. A recent study among Ugandan HIV-infected patients receiving medical care with The AIDS Support Organization (TASO) at Mulago hospital, found that among patients with psychological distress, 27 % of these had generalized anxiety disorder and 27 % had panic disorder [68]. An earlier study conducted by Petrushkin and colleagues in 2005 had estimated panic disorder at 32.6 % in HIV-positive patients [69].

The risk factors that have been associated with development of anxiety disorders include (i) HIV-positive diagnosis: unexpected positive test result especially with no or poor pre-test counseling, late diagnosis, late stage of HIV/AIDS, (ii) lack of

social support, (iii) past sexual abuse, (iv) living in a conflict/post-conflict society, (v) violence and especially partner violence, (vi) substance abuse, (vii) poor pre-infection psychological adjustment, for example, personality disorder, past affective disorder,(viii) poor access to care: absent or inconsistent HIV care, (ix) poor economic support: unemployment, poverty, (x) loss of significant others: partner, spouse, child, parent (orphan-hood, widow, etc.) and (xi) lastly, stigma and the presence of other diseases of stigma [68, 70].

Researchers have also described AIDS phobia, obsessive compulsive disorder and post-traumatic stress disorder (PTSD) as commonly found in HIV/AIDS. PTSD has particularly been associated with the sudden news of a positive HIV test (especially where there was no pre-test counseling), past sexual abuse and living in conflict/post-conflict communities in Africa in which HIV/AIDS is often co morbid with war-related PTSD [70, 71].

Post-traumatic Stress Disorder (PTSD)

PTSD may precede an HIV diagnosis due to previously experienced traumatic events, or may emerge post-HIV diagnosis as a result of the stress of being diagnosed with a life-threatening illness [72, 73] or subsequent challenges over the course of the HIV disease trajectory. Stresses include fears and worries about physical decline and disability, access to appropriate treatment, the welfare of dependents, loss of employment, stigma, discrimination, possible isolation, and dying or traumatic events.

Available studies from Africa suggest that the lifetime prevalence of PTSD among PLWHA ranges from 30 % to 64 %. Among recently diagnosed HIV-positive South African individuals, an estimated PTSD rate of 15 % and 26 % was determined at baseline and follow-up, respectively [74] compared to the South African general population lifetime and 12 month prevalence of PTSD of 2.3 % and 0.6 %, respectively [75, 76]. Among the 15 % who met criteria at baseline for PTSD, patients reported as their index trauma in decreasing order, being informed of their HIV-positive diagnosis (36 %), being raped (23 %), being robbed or assaulted (14 %), being the victim of intimate partner violence (9 %), experiencing a serious accident (9 %) and the death of someone close to the individual (9 %) [13, 77]. Another South African study found a lifetime PTSD rate of 54 % and an incidence of HIV-related PTSD of 40 % [73].

Psychosis

Psychotic symptoms may be part of a major depressive disorder, schizophrenia, mania, obsessive-compulsive disorder, medication side effects, or secondary to drug or alcohol abuse, CNS complications, or medications. Thus, the pathophysiology of psychosis in HIV infection is complex, and a multifactorial etiology of psychotic symptoms is likely in many cases. However, there are many reports of psychotic symptoms in

HIV-infected persons in the absence of concurrent substance abuse, iatrogenic causes, evidence of opportunistic infection or neoplasm, or detectable cognitive impairment. These usually present atypically and with paranoia, as a common symptom in clear consciousness [71]. A common clinical feature of new onset psychosis in HIV-infected patients is the acute onset of HIV symptoms. In one Ugandan study, researchers found that HIV infection worsens neuropsychological impairment among individuals with psychosis which persists even during the euthymic state. Nakasujja and her colleagues (2012) compared cognitive function in HIV positive and HIV negative individuals in a cohort of individuals with psychosis [78]. The cognitive impairment was more pronounced among the HIV positive individuals and especially so for the females. Although earlier studies indicated that cognitive impairment and psychosis were late manifestations of HIV disease [79, 80] studies from Low and Middle Income Countries, LMICs show that the two conditions can sometimes occur early as evidenced by the moderate level of CD4 count and the intermediate WHO stages of disease manifestation [61].

Sero-prevalence of HIV in Severe Mental Illness (SMI) Populations

Again, most studies of HIV sero-prevalence in individuals living with SMI have been undertaken in HICs. A systematic review of such studies showed HIV sero-prevalence rates ranging from 3 % to 23 % among patients with SMI [70]. The higher HIV sero-prevalence rates among people with SMI in sub-Saharan African countries including Zimbabwe [81, 82], Uganda [83], and South Africa [84, 85] have underscored the importance of giving particular attention to HIV prevention among people with SMI in sub-Saharan Africa [8].

Risk Behaviors in SMI

Individuals with SMI, particularly those with mood disorders, engage in high rates of sexual risk behaviors associated with HIV infection, including multiple sex partners, unprotected intercourse, and sex trade [86]. Research on the mechanisms underlying the association between pre-existing mental disorders and HIV infection is limited. However, it has been hypothesized that symptoms such as impulsivity, disinhibition, poor judgment and hyper sexuality may predispose affected individuals to risky behaviors such as unsafe sexual practices resulting in acquisition of HIV infection [87].

Previous epidemiological studies conducted in developed countries make clear that persons living with an SMI are more likely to be victims of sexual coercion and intimate partner violence, to live in risky environments, to have unstable partnerships in high-risk sexual networks, to use substances that impair decision making, and to lack the emotional stability, judgment, and interpersonal skills needed to avoid risk [88].

Data emerging from sub-Saharan African countries and other LMICs reports a wide range of HIV risk sexual behaviors. A recent qualitative study in Uganda showed that SMI exacerbated sexual vulnerability in the women by contributing to casual sex, to exploitative and non-monogamous sexual relationships, and to sexual assault by non-partners [89]. Studies from Brazil showed that high rates of lifetime unprotected sex, substance use and, early sexual initiation are associated with SMI [74, 90].

Impact of SMI on Health Outcomes

In Uganda, HIV positive individuals with SMI are often denied access to ART in general hospital settings and research studies [18] because of presumed inability to adequately adhere or tolerate treatment. However, recent efforts to scale up antiretroviral therapy (ART) led to the establishment of an ART program at the Butabika National Referral Mental Hospital. A recent study found that SMI at ART initiation was associated with worse retention in HIV care, specifically over the first 6 months [91]. This finding suggests that early interventions to support and maintain these individuals in care are needed for individuals with HIV and SMI who are initiating ART.

In South Africa, a cross-sectional retrospective folder review of 100 PLWH suffering from an SMI revealed that 63 did not attend a first 6-month HIV clinic follow-up. There were no significant differences between 6-month attenders and non-attenders on demographic or clinical variables. After adjustment, respondents who had been re-admitted to a psychiatric hospital more than once were more likely not to attend their follow-up visit compared to those with no re-admissions. These findings suggest that PLWH who have a co-morbid SMI are an especially vulnerable group of patients [92].

Despite the much vulnerability among individuals with SMI, HIV prevention and treatment programs in LMICs do not consider them as one of the most at-risk populations (MARPs) and thus, remain the most understudied vulnerable group in the HIV epidemic [93]. Recent evidence in high income countries, HICs, suggests that specialized programmes and services for serious mental illness and HIV-positive individuals have resulted in HIV care that is as good, and in some ways better than other HIV patients without SMI [94, 95]. Thus, targeted culturally sensitive HIV prevention programs [96] for individuals with SMI in LMICs should be a priority in stemming the HIV epidemic.

Conclusion

To begin the process of any HIV care, routine HIV testing coupled with pre- and post-test counseling should be offered to patients accessing outpatient and inpatient mental health services. Psychiatric assessment should always be incorporated into any assessment of patients with HIV/AIDS. Referral networks to other healthcare

facilities should be put in place so that medical assessments to rule out organic causes can be treated. Mental health care providers should be equipped with skills and tools to provide prevention interventions for persons living with mental disorder and HIV/AIDS [97]. Likewise, HIV healthcare personnel need to be equipped with skills and tools to be able to carry out routine mental health assessments/screening for the common mental health problems in HIV/AIDS.

Lastly, HIV infection causes significant brain degeneration with resultant affective (depression, mania), psychotic, anxiety and cognitive disorders, the latter commonly referred to as HIV-Associated neurocognitive disorders or HAND. These neuropsychiatric disorders occur in both children and adults. Untreated, they will compromise adherence to treatment initiatives and pose significant HIV-infection risk behavior. All this calls for integration of mental health care in any HIV-care program for their early detection and treatment for better outcomes and improved quality of life for PLWHA and for prevention strategies if we are to stem the epidemic.

References

1. World-Health-Organization. The global burden of disease: 2008 update. Geneva; 2008.
2. Prince M, et al. No health without mental health. Lancet. 2007;370(9590):859–77.
3. Gallego L, Barreiro P, Lopez-Ibor JJ. Diagnosis and clinical features of major neuropsychiatric disorders in HIV infection. AIDS Rev. 2011;13(3):171–9.
4. Hendershot CS, et al. Alcohol use and antiretroviral adherence: review and meta-analysis. J Acquir Immune Defic Syndr. 2009;52(2):180–202.
5. Gonzalez JS, et al. Depression and HIV/AIDS treatment nonadherence: a review and meta-analysis. J Acquir Immune Defic Syndr. 2011;58(2):181–7.
6. Olley BO, Seedat S, Stein DJ. Psychopathology and coping in recently diagnosed HIV/AIDS patients. S Afr Med J (Suid-Afrikaanse tydskrif vir geneeskunde). 2004;94(9):720, 722.
7. Cournos F, McKinnon K, Wainberg M. What can mental health interventions contribute to the global struggle against HIV/AIDS? World Psychiatry. 2005;4(3):135–41.
8. Collins PY, et al. What is the relevance of mental health to HIV/AIDS care and treatment programs in developing countries? A systematic review. AIDS. 2006;20(12):1571–82.
9. Maj M, et al. WHO neuropsychiatric AIDS study, cross-sectional phase I. Study design and psychiatric findings. Arch Gen Psychiatry. 1994;51(1):39–49.
10. Pearson CR., MA. Micek J, Pfeiffer P, Montoya E, Matediane T, Jonasse A, Cunguara D, Rao SS, Gloyd. "One year after ART initiation: psychosocial factors associated with stigma among HIV-positive Mozambicans." AIDS and Behavior. 2009;13(6):1189–96.
11. Cohen MH, Fabri M, Cai X, Shi Q, Hoover DR, Binagwaho A, Culhane MA, Mukanyonga H, Karegeya DK, Anastos K. Prevalence and predictors of posttraumatic stress disorder and depression in HIV-infected and at-risk Rwandan women. J Womens Health (Larchmt). 2009;18(11):1783–91.
12. Adewuya AO, Afolabi MO, Ola BA, Ogundele OA, Ajibare AO, Oladipo BF, Fakande I. Relationship between depression and quality of life in persons with HIV infection in Nigeria. Int J Psychiatry Med. 2008;38(1):43–51.
13. Olley BO, Seedat S, Stein DJ. Persistence of psychiatric disorders in a cohort of HIV/AIDS patients in South Africa: a 6-month follow-up study. J Psychosom Res. 2006;61(4):479–84.
14. Spies G, Kader K, Kidd M, Smit J, Myer L, Stein DJ, et al. Validity of the K-10 in detecting DSM-IV-defined depression and anxiety disorders among HIV-infected individuals. AIDS Care. 2009;21(9):1163–8.

15. Nakimuli-Mpungu E, et al. Clinical presentation of bipolar mania in HIV-positive patients in Uganda. Psychosomatics. 2009;50(4):325–30.
16. Nakasujja N, Skolasky RL, Musisi S, Allebeck P, Robertson K, Ronald A, et al. Depression symptoms and cognitive function among individuals with advanced HIV infection initiating HAART in Uganda. BMC Psychiatry. 2010;10(1):44.
17. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. Lancet. 1997;349(9064):1498–504.
18. Rabkin JG. HIV and depression: 2008 review and update. Curr HIV/AIDS Rep. 2008;5(4): 163–71.
19. Etienne M, et al. Indicators of adherence to antiretroviral therapy treatment among HIV/AIDS patients in 5 African countries. J Int Assoc Physicians AIDS Care. 2010;9(2):98–103.
20. Kagee A, Martin L. Symptoms of depression and anxiety among a sample of South African patients living with HIV. AIDS Care. 2010;22(2):159–65.
21. Marwick KF, Kaaya SF. Prevalence of depression and anxiety disorders in HIV-positive outpatients in rural Tanzania. AIDS Care. 2010;22(4):415–9.
22. Myer L, et al. The mental health impact of AIDS-related mortality in South Africa: a national study. J Epidemiol Community Health. 2009;63(4):293–8.
23. Bass JK, Bolton PA, Murray LK. Do not forget culture when studying mental health. Lancet. 2007;370(9591):918–9.
24. Ferrando SJ, Freyberg Z. Treatment of depression in HIV positive individuals: a critical review. Int Rev Psychiatry. 2008;20(1):61–71.
25. Nakimuli-Mpungu E, Katabira E, Nachega JB, Musisi S, Bass J. Prevalence and factors associated with depressive disorders in an HIV + rural patient population in southern Uganda. J Affect Disord. 2011. 10.1016/j.jad.2011.07.009.
26. Byakika-Tusiime J, Crane J, Oyugi JH, Ragland K, Kawuma A, Musoke P, Bangsberg DR. Longitudinal antiretroviral adherence in HIV+ Ugandan parents and their children initiating HAART in the MTCT-Plus family treatment model: role of depression in declining adherence over time. AIDS Behav. 2009;13 Suppl 1:82–91.
27. Peltzer K, Friend-du Preez N, Ramlagan S, Anderson J. Antiretroviral treatment adherence among HIV patients in KwaZulu-natal, South Africa. BMC Public Health. 2010;10:111.
28. Adewuya AO, Afolabi MO, Ola BA, Ogundele OA, Ajibare AO, Oladipo BF, Fakande I. The effect of psychological distress on medication adherence in persons with HIV infection in Nigeria. Psychosomatics. 2010;51(1):68–73.
29. Amberbir A, Woldemichael K, Getachew S, Girma B, Deribe K. Predictors of adherence to antiretroviral therapy among HIV-infected persons: a prospective study in southwest Ethiopia. BMC Public Health. 2008;8:265.
30. Bunnell RE, Nassozi J, Marum E, Mubangizi J, Malamba S, Dillon B, Kalule J, Bahizi J, Musoke N, Mermin JH. Living with discordance: knowledge, challenges, and prevention strategies of HIV-discordant couples in Uganda. AIDS Care. 2005;17(8):999–1012.
31. Murray LK, Semrau K, McCurley E, Thea DM, Scott N, Mwiya M, Kankasa C, Bass J, Bolton P. Barriers to acceptance and adherence of antiretroviral therapy in urban Zambian women: a qualitative study. AIDS Care. 2009;21(1):78–86.
32. Nakimuli-Mpungu E, Mojtabai R, Alexandre P, Musisi S, Katabira E, Nachega JB, Tresman G, Bass JK. Lifetime depressive disorders and adherence to anti-retroviral therapy in a rural HIV clinic in southern Uganda: a case-control study. J Affct Disord. 2012. doi:10.1016/j.jad.2011.07.009.
33. Bradley MV, Remien RH, Dolezal C. Depression symptoms and sexual HIV risk behavior among serodiscordant couples. Psychosom Med. 2008;70(2):186–91.
34. Kelly JA, et al. Factors associated with severity of depression and high-risk sexual behavior among persons diagnosed with human immunodeficiency virus (HIV) infection. Health Psychol. 1993;12(3):215–9.
35. Ickovics JR, et al. Mortality, CD4 cell count decline, and depressive symptoms among HIV-seropositive women: longitudinal analysis from the HIV Epidemiology Research Study. JAMA. 2001;285(11):1466–74.

36. Leserman J, et al. Relation of lifetime trauma and depressive symptoms to mortality in HIV. Am J Psychiatry. 2007;164(11):1707–13.
37. Kacanek D, et al. Incident depression symptoms are associated with poorer HAART adherence: a longitudinal analysis from the Nutrition for Healthy Living study. J Acquir Immune Defic Syndr. 2010;53(2):266–72.
38. Carrieri MP, et al. Failure to maintain adherence to HAART in a cohort of French HIV-positive injecting drug users. Int J Behav Med. 2003;10(1):1–14.
39. Horberg MA, et al. Effects of depression and selective serotonin reuptake inhibitor use on adherence to highly active antiretroviral therapy and on clinical outcomes in HIV-infected patients. J Acquir Immune Defic Syndr. 2008;47(3):384–90.
40. Chesney M. Adherence to HAART regimens. AIDS Patient Care STDS. 2003;17(4):169–77.
41. Bangsberg DR. Preventing HIV antiretroviral resistance through better monitoring of treatment adherence. J Infect Dis. 2008;197 Suppl 3:S272–8.
42. Kozal MJ, et al. HIV drug resistance and HIV transmission risk behaviors among active injection drug users. J Acquir Immune Defic Syndr. 2005;40(1):106–9.
43. Pence BW, O'ÄôDonnell JK, Gaynes BN. Falling through the cracks: the gaps between depression prevalence, diagnosis, treatment, and response in HIV care. AIDS. 2012;26(5):656–8. doi:10.1097/QAD.0b013e3283519aae.
44. Wagner GJ. Predictors of antiretroviral adherence as measured by self-report, electronic monitoring, and medication diaries. AIDS Patient Care STDS. 2002;16(12):599–608.
45. Nilsson Schonnesson L, et al. Factors associated with suboptimal antiretroviral therapy adherence to dose, schedule, and dietary instructions. AIDS Behav. 2007;11(2):175–83.
46. Ammassari A, et al. Depressive symptoms, neurocognitive impairment, and adherence to highly active antiretroviral therapy among HIV-infected persons. Psychosomatics. 2004;45(5):394–402.
47. Hartzell JD, Janke IE, Weintrob AC. Impact of depression on HIV outcomes in the HAART era. J Antimicrob Chemother. 2008;62(2):246–55.
48. Cook JA, et al. Depressive symptoms and AIDS-related mortality among a multisite cohort of HIV-positive women. Am J Public Health. 2004;94(7):1133–40.
49. Bouhnik AD, et al. Depression and clinical progression in HIV-infected drug users treated with highly active antiretroviral therapy. Antivir Ther. 2005;10(1):53–61.
50. Ironson G, et al. Psychosocial factors predict CD4 and viral load change in men and women with human immunodeficiency virus in the era of highly active antiretroviral treatment. Psychosom Med. 2005;67(6):1013–21.
51. Asch SM, et al. Underdiagnosis of depression in HIV: who are we missing? J Gen Intern Med. 2003;18(6):450–60.
52. Schmidt U, Miller D. Two cases of hypomania in AIDS. Br J Psychiatry. 1988;152:839–42.
53. Brouillette MJ, Chouinard G, Lalonde R. Didanosine-induced mania in HIV infection (letter). Am J Psychiatry. 1994;151:1839–40.
54. Wright JM, Sachder PS, Perkins RJ, Rodriguez P. Zidovudine-related mania. Med J Aust. 1989;15:334–41.
55. Maxwell S, Scheftner WA, Kessler MA, Busch K. Manic syndromes associated with zidovudine therapy (letter). JAMA. 1988;259:3406–7.
56. Johannessen DJ, Wilson LG. Mania with cryptococcal meningitis in two AIDS patients. J Clin Psychiatry. 1988;49:200–1.
57. Lyketsos CG, Schwartz J, Fishman M, Treisman G. AIDS mania. J Neuropsychiatr Clin Neurosci. 1997;9:277–9.
58. Kieburtz K, Zettelmaier AE, Ketonen L, Tuite M, Caine ED. Manic syndrome in AIDS. Am J Psychiatry. 1991;148:1068–70.
59. Lyketsos CG, Hanson AL, Fishman M, Rosenblatt A, McHugh PR, Treisman GJ. Manic syndrome early and late in the course of HIV. Am J Psychiatry. 1993;150:326–7.
60. Ellen SR, Judd FK, Mijch AM, Cockram A. Secondary mania in patients with HIV infection. Aust N Z J Psychiatry. 1999;3:353–60.

61. Nakimuli-Mpungu E, Musisi S, Kiwuwa-Mpungu S, Katabira E. Early-onset versus late-onset HIV-related secondary mania in Uganda. Psychosomatics. 2008;49(6):530–4.
62. Mijch AM, Judd FK, Lyketsos CG, Ellen S, Cockram A. Secondary mania in patients with HIV infection: are antiretroviral drugs effective? J Neuropsychiatr Clin Neurosci. 1999;11: 475–80.
63. Nakimuli-Mpungu E, Musisi S, Kiwuwa S, et al. Primary mania versus HIV-related secondary mania in Uganda. Am J Psychiatry. 2006;163:1349–54.
64. Kupler DJ, Frank E, Grochocinski VJ, et al. African-American participants in a bipolar disorder registry: clinical and treatment characteristics. Bipolar Disord. 2005;7:82–8.
65. Perretta P, Akiskai HS, Nisita C, et al. The high prevalence of bipolar II and associated cyclothymic and hyperthymic temperatures in HIV-positive patients. J Affect Disord. 1998;50:215–24.
66. Joint United Nations Program on HIV/AIDS, World Health Organization. AIDS epidermic update: December 2005. Publication UN-AIDS/05.19E. Geneva, UNAIDS; 2005. Available at http://www.unaids.org/epi/2005/doc/EPlupdate2005_html_en/epi05_00_en.htm
67. Smith DJ, Muir WJ, Blackwood DHR. Neurocognitive impairment in euthymic young adults with bipolar spectrum disorder. Bipolar Disord. 2006;8:40–6.
68. Kuganda S. M.Med thesis (psychiatry). Kampala: Makerere University College of Health Sciences; 2011.
69. Petrushkin A, Boardman J, Ovuga E. Psychiatric disorders in HIV- positive individuals in urban Uganda. Psychiatr Bull. 2005;29:455–58.
70. Weiser SD, Wolfe WR, Bangsberg DR. The HIV epidemic among individuals with mental illness in the United States. Curr Infect Dis Rep. 2004;6(5):404–10.
71. Musisi S, Kinyanda E, editors. Psychiatric problems of HIV/AIDS and their management in Africa. Kampala: Fountain Publishers; 2009.
72. Breslau N, Kessler RC. The stressor criterion in DSM-IV posttraumatic stress disorder: an empirical investigation. Biol Psychiatry. 2001;50(9):699–704.
73. Martin L, Kagee A. Lifetime and HIV-related PTSD among persons recently diagnosed with HIV. AIDS Behav. 2011;15(1):125–31.
74. Guimaraes MD, McKinnon K, Campos LN, Melo AP, Wainberg M. HIV risk behavior of psychiatric patients with mental illness: a sample of Brazilian patients. Rev Bras Psiquiatr. 2010;32(4):351–60.
75. Williams DR, et al. Twelve-month mental disorders in South Africa: prevalence, service use and demographic correlates in the population-based South African Stress and Health Study. Psychol Med. 2008;38(2):211–20.
76. Stein DJ, et al. Lifetime prevalence of psychiatric disorders in South Africa. Br J Psychiatry J Ment Sci. 2008;192(2):112–7.
77. Olley BO, et al. Post-traumatic stress disorder among recently diagnosed patients with HIV/AIDS in South Africa. AIDS Care. 2005;17(5):550–7.
78. Nakasujja N, Allebeck P, Agren H, Musisi S, Katabira E. Cognitive dysfunction among HIV positive and HIV negative patients with psychosis in Uganda. PLoS One. 2012;7(9):e44415.
79. el-Mallakh RS. HIV-related psychosis. J Clin Psychiatry. 1992;53(8):293–4.
80. Sewell DD, Jeste DV, Atkinson JH, Heaton RK, Hesselink JR, Wiley C, et al. HIV-associated psychosis: a study of 20 cases. San Diego HIV neurobehavioral research center group. Am J Psychiatry. 1994;151(2):237–42.
81. Acuda SW, Sebit MB. Serostatus surveillance testing of HIV-I infection among Zimbabwean psychiatric inpatients, in Zimbabwe. Cent Afr J Med. 1996;42(9):254–7.
82. Acuda SW, Sebit MB. Prevalence of psychoactive substance use among psychiatric in-patients in Harare, Zimbabwe. Cent Afr J Med. 1997;43(8):226–9.
83. Maling S, Todd J, Van der Paal L, Grosskurth H, Kinyanda E. HIV-1 seroprevalence and risk factors for HIV infection among first-time psychiatric admissions in Uganda. AIDS Care. 2011;23(2):171–8.
84. Singh D, Berkman A, Bresnahan M. Seroprevalence and HIV-associated factors among adults with severe mental illness – a vulnerable population. S Afr Med J. 2009;99(7):523–7.

85. Collins PY, Berkman A, Mestry K, Pillai A. HIV prevalence among men and women admitted to a South African public psychiatric hospital. AIDS Care. 2009;21(7):863–7.
86. Meade CS, Sikkema KJ. HIV risk behavior among adults with severe mental illness: a systematic review. Clin Psychol Rev. 2005;25(4):433–57.
87. Meade CS, Fitzmaurice GM, Sanchez AK, Griffin ML, McDonald LJ, Weiss RD. The relationship of manic episodes and drug abuse to sexual risk behavior in patients with co-occurring bipolar and substance use disorders: a 15-month prospective analysis. AIDS Behav. 2011;15(8):1829–33.
88. Carey MP, Carey KB, Kalichman SC. Risk for human immunodeficiency virus (HIV) infection among persons with severe mental illnesses. Clin Psychol Rev. 1997;17(3):271–91.
89. Lundberg P, Johansson E, Okello E, Allebeck P, Thorson A. Sexual risk behaviours and sexual abuse in persons with severe mental illness in Uganda: a qualitative study. PLoS One. 2012;7(1):e29748.
90. Melo AP, Cesar CC, AcurcioFde A, Campos LN, Ceccato M, Wainberg ML, et al. Individual and treatment setting predictors of HIV/AIDS knowledge among psychiatric patients and their implications in a national multisite study in Brazil. Community Ment Health J. 2010;46(5):505–16.
91. Nachega JB, Mutamba B, Basangwa D, Nguyen H, Dowdy DW, Mills EJ, et al. Severe mental illness at ART initiation is associated with worse retention in care among HIV-infected Ugandan adults. Trop Med Int Health. 2013;18(1):53–7.
92. Joska JA, Obayemi Jr A, Cararra H, Sorsdahl K. Severe mental illness and retention in antiretroviral care: a retrospective study. AIDS Behav. 2014;18:1–9.
93. Ngwena J. HIV/AIDS awareness in those diagnosed with mental illness. J Psychiatr Ment Health Nurs. 2011;18(3):213–20.
94. Bogart LM, Fremont AM, Young AS, Pantoja P, Chinman M, Morton S, et al. Patterns of HIV care for patients with serious mental illness. AIDS Patient Care STDS. 2006;20(3):175–82.
95. Himelhoch S, Brown CH, Walkup J, Chander G, Korthius PT, Afful J, et al. HIV patients with psychiatric disorders are less likely to discontinue HAART. AIDS. 2009;23(13):1735–42.
96. Agenor M, Collins PY. Preventing HIV among U.S. women of color with severe mental illness: perceptions of mental health care providers working in urban community clinics. Health Care Women Int. 2013;34(3–4):281–302.
97. Collins PY. Challenges to HIV prevention in psychiatric settings: perceptions of South African mental health care providers. Soc Sci Med. 2006;63(4):979–90.

Part III
Pediatric Brain Degenerations in Uganda

Chapter 11
Children with Neurodegenerative Development Disorders in Uganda

Angelina Kakooza-Mwesige and Dirk M. Dhossche

Abstract Neurodegenerative disorders in childhood are a miscellaneous group of severe disorders characterized by regression and progressive neurological degeneration with impairment of vision, hearing, speech or movement often associated with seizures, feeding difficulties and impairment of intellect. The course can be acute, rapidly progressive or slowly progressive, only disclosing its full impact over time. Neurodegenerative diseases have multiple causes including metabolic, viral, immunopathic, environmental and epileptogenic, but many lack an identifiable biochemical or metabolic cause or mechanism. Neurodegenerative disorders are an important source of childhood impairment in developing countries like Uganda due to the high prevalence of specific causes such as human immunodeficiency virus, cerebral malaria, sub-acute sclerosing panencephalitis due to measles, and the emergence of poorly understood entities such as Nodding Syndrome. Knowledge on this extremely varied group is expanding along with biochemical and genetic advances but there is currently a paucity of data in most low and middle income settings including Uganda on the number of children affected by neurodegenerative disorders and their demographic characteristics. The detection and diagnosis of childhood neurodegenerative disorders is complex and fraught with pitfalls. There is need to incorporate a rigorous history, including family history, and physical examination as an indispensable component of the diagnostic evaluation. Neurodegenerative disorders may be mistaken at the disease onset for unexplained psychiatric disturbance, cerebral palsy, epilepsy or cognitive impairment. Laboratory investigations, neuroimaging and specific tests assist in making an accurate diagnosis which is important for appropriate therapy, prognosis, and genetic counseling. Often the treatment is symptomatic but dietary restrictions may be useful in certain diseases as well as specific treatments to counteract the offending metabolites, improve or decrease abnormal enzyme function, or to off-set metabolic dysfunction. It may be possible

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S. Musisi, S. Jacobson (eds.), *Brain Degeneration and Dementia in Sub-Saharan Africa*, DOI 10.1007/978-1-4939-2456-1_11

in the future to target specific pathways with somatic gene therapy but this will require more technological advances and discoveries. A referral for genetic counseling is important due to heritability of many neurodegenerative disorders. Public health initiatives should focus on the risk of consanguineous marriages as a way to raise awareness of a preventable cause of a neurodegenerative disorder in childhood.

Keywords Neurodegenerative disorders • Neurodevelopmental disorders • Childhood • Regression

Abbreviations

BBB	Blood-brain barrier
CNS	Central nervous system
CSF	Cerebral spinal fluid
ECG	Electrocardiogram
EEG	Electroencephalogram
ERG	Electroretinogram
HAART	Highly active antiretroviral therapy
HIC	High income countries
LMIC	Low and middle income countries
NDDD's	Neurodegenerative developmental disorders
NS	Nodding syndrome
SSPE	Subacute sclerosing panencephalitis

Introduction

Neurodevelopmental disorders have been singled out as one of the greatest challenges to improving global public health by the World Health Organization (WHO) [1]. Neurodevelopmental disorders comprise a miscellaneous group of chronic conditions, often severe, that commence during neurological development and typically persist throughout the life of an affected child. These include the following specific conditions: cognitive impairment, learning disorders, cerebral palsy, autism spectrum disorders, epilepsy, attention deficit hyperactivity disorders, hearing impairment, visual impairment and neuromuscular disorders.

A small group of children is afflicted with neurodegenerative disorders, a severe type of disorder characterized by regression and progressive neurological degeneration that can occur acutely, rapidly progressive, or slowly progressive only disclosing its full impact over time. Neurodegenerative diseases have multiple causes, including metabolic, viral, immunologic, environmental and epileptogenic, but

many lack an identifiable biochemical or metabolic cause or mechanism. Knowledge on this extremely varied group is expanding along with biochemical and genetic advances and will be discussed in this chapter.

Neurodegeneration denotes the progressive loss of structure and function of neurons from the central or peripheral nervous system [2]. This evolving loss of neurons produces the neurodegenerative developmental disorders (NDDD's) by causing the child's brain to degenerate and results in severe cognitive impairment or death [3]. These neurodegenerative disorders of childhood include a large, diverse group of diseases that develop as a consequence of certain genetic and biochemical defects, chronic viral infections, and miscellaneous unidentified causes.

There is paucity of data in most low and middle income settings including Uganda on the number of children affected by NDDD's and their demographic characteristics. Furthermore the diagnosis of these conditions is often impeded by the perplexing nature of presentation which is comparable to the common pediatric problems such as failure to thrive, recurrent vomiting, feeding problems, sepsis and/or developmental delay [4]. In addition, NDDD's may be mistaken at their onset for unexplained psychiatric disturbance, cerebral palsy, epilepsy or cognitive impairment. This implies that one has to have a high index of suspicion and sum up all the important clinical information so that the appropriate investigations are carried out. Furthermore it stresses the importance of obtaining a thorough history and physical examination as a precondition to undertaking extensive investigations in these disorders. The aim of this chapter is to present an overview of some of the causes of neurodegenerative disorders and their presentation as seen in Ugandan children.

Epidemiology

Neurodegenerative disorders are a small but severe subgroup within the neurodevelopmental disorders. Research on neurodegenerative disorders in childhood is limited in Uganda and in most other developing countries yet there are emerging data on the whole group of neurodevelopmental disorders. The available data on some neurodevelopmental disorders will be presented here. Data on specific and common etiologies such as human immunodeficiency virus, cerebral malaria, sub-acute sclerosing panencephalitis, and Nodding syndrome will be presented later in the text.

Neurodevelopmental disorders among children have been extensively researched in High Income Countries (HIC) but there is limited information on them in Low and Middle Income Countries (LMIC) because there are hardly any studies measuring the prevalence of these disorders, and none measuring changes over time. It is believed that neurodevelopmental disorders are more common in Low and Middle Income Countries (LMIC) than in the High Income Countries (HIC) due to multiple known risk factors such as malaria, HIV and other infectious diseases. However with the advent of effective prevention and treatment of infectious diseases, control of toxic exposures and nutritional deficiencies there has been a significant lowering of the childhood mortality over the last decade [5]. This implies that there will likely

be an expected increase in prevalence of children with neurodevelopmental disorders as the mortality is higher in such children compared with the typically developing ones [6]. This hypothesis however needs to be supported by further studies.

A three stage community based survey conducted in rural and urban areas of Uganda to study the prevalence of neurodevelopmental disorders screened 1,169 children aged 2–9 years focusing on seven conditions namely: cognitive impairment, cerebral palsy, autism spectrum disorders, epilepsy, speech and language disorders, hearing impairment and vision impairment. A prevalence of 10.3–12.8/100 population was reported [7]. Of these the most common neurodevelopmental disorder was moderate-severe cognitive impairment (26.2 %), followed by epilepsy (10.6 %) and speech and language impairment (8.6 %). The estimated prevalence for Autism was 1.2/100–1.3/100 children in this population [7] There is scanty information on the basic descriptive epidemiology of neurodegenerative developmental disorders (NDDD's) in childhood, particularly in LMIC. Currently available data from LMIC is often based on case series from referral hospitals or designated community studies and as such, is neither representative of the larger geographic region, nor of the whole spectrum of NDDD's.

In general, NDDD's are rare in the pediatric population and are estimated to occur in 1/10,000–1/500,000 of the population in the HIC [8]. In the few studies done earlier in Africa focusing on varied disease conditions the prevalence ranged from 4.8/100,000 to 10/100,000 [9, 10]. The varied aspects regarding these conditions among children in Uganda remain obscure. Nevertheless, it is known that as a group of diseases they confer an enormous burden in terms of human suffering and economic cost on the child, the family and the community [11].

Diagnosis

A specific biochemical or genetic defect does not wholly ascertain the diagnosis of a NDDD. There is need to incorporate a rigorous history and physical examination as an indispensable component of the diagnostic evaluation. The characteristic of a neurodegenerative disorder is regression and progressive deterioration of neurologic function with impairment of vision, hearing, speech or movement often associated with seizures, feeding difficulties and impairment of intellect. Reaching a specific diagnosis is important for providing appropriate therapy, prognosis and genetic counseling. The inheritance pattern of several neurodegenerative disorders is autosomal recessive, and therefore consanguinity is considered a risk factor that should be addressed when counseling families and raising awareness through public health policy [12]. Examples of some neurodegenerative disorders, the time of presentation, inheritance pattern and associated features are shown in Tables 11.1, 11.2, and 11.3.

Table 11.1 Some neurodegenerative disorders in neonates showing the principal systems affected, neurologic/psychiatric/behavioral abnormalities and their inheritance patterns

Neurodegenerative disorder	System involved	Neurologic/psychiatric/behavioral abnormalities	Inheritance pattern
Infantile Refsum's disease	Peroxisomal disorders	Rapid, jerky eye movements (nystagmus); progressive muscle weakness and wasting; poor balance and coordination (ataxia); hearing loss	Austosomal recessive
Zellweger syndrome	Peroxisomal disorders	Weak muscle tone (hypotonia), feeding problems, hearing loss, vision loss, and seizures	Austosomal recessive
Neonatal adrenoleukodystrophy	Peroxisomal disorders	Hypotonia, vision problems, hearing loss, liver dysfunction, developmental delay, intellectual disability	Austosomal recessive
Ornithine transcarbamoylase deficiency	Urea cycle disorders	Feeding difficulties, lethargy, and respiratory distress, irritability, temper tantrums, inconsolable crying, ataxia, seizures, hyperactivity	X-linked recessive
Argininosuccinicaciduria	Urea cycle disorders	Feeding difficulties, lethargy, mental retardation, recurrent generalized convulsions, ataxia, poorly controlled breathing rate or body temperature	Austosomal recessive
Arginosuccinate lyase deficiency	Urea cycle disorders	Lethargy, poor feeding, neurocognitive deficiencies (attention deficit hyperactivity disorder) [ADHD], developmental disability, seizures, and learning disability	Austosomal recessive
Pyruvate carboxylase deficiency	Mitochondrial disorders	Weak muscle tone (hypotonia), abnormal movements, seizures, and coma	Autosomal recessive
Glutaricaciduria type II deficiency	Mitochondrial disorders	Poor feeding and decreased activity, and vomiting	Autosomal recessive
Carnitine palmitoyltransferase deficiency type II	Mitochondrial disorders	Seizures, cardiomyopathy, respiratory failure, seizures, liver failure, cardiomyopathy, and an irregular heartbeat (arrhythmia)	Autosomal recessive
Maple syrup urine disease	Amino acid and organic acid disorders	Intermittent periods of ataxia, drowsiness, behaviour disturbances, and seizures	Autosomal recessive
Nonketotic hyperglycemia	Amino acid and organic acid disorders	Lethargy, profound hypotonia, intractable generalized or myoclonic seizures, apnea, feeding difficulties	Autosomal recessive

(continued)

Table 11.1 (continued)

Neurodegenerative disorder	System involved	Neurologic/psychiatric/behavioral abnormalities	Inheritance pattern
Methylmalonic acidemia	Amino acid and organic acid disorders	Hypotonia, lethargy, recurrent vomiting, profound metabolic acidosis, spastic quadriparesis, dystonia, and severe developmental delay	Autosomal recessive
Menkes kinky hair syndrome	Copper transport system	Weak muscle tone (hypotonia), sagging facial features, seizures, developmental delay, and intellectual disability	X linked recessive
Spinal muscular atrophy type 1	Peripheral nerves	Muscle weakness, respiratory failure, a weak cry; problems feeding; recurrent episodes of pneumonia, excessive sweating (hyperhidrosis), loss of bladder and bowel control, and an irregular heartbeat (arrhythmia)	Autosomal recessive
Smith-Lemli-Opitz syndrome	Cholesterol metabolism	Microcephaly, moderate-severe intellectual disability, Autistic behaviours, hyperactivity, aggressiveness and self injurious behaviours weak muscle tone (hypotonia), feeding difficulties, sleep cycle disturbance	Autosomal recessive
Galactosemia type I	Carbohydrate metabolism	Poor feeding, delayed development, clouding of the lens of the eye (cataract), speech difficulties, and intellectual disability	Autosomal recessive

Table 11.2 Some neurodegenerative disorders in infancy showing the principal systems affected, neurologic/psychiatric/behavioral abnormalities and their inheritance patterns

Neurodegenerative disorder	System involved	Neurologic/psychiatric/behavioral abnormalities	Inheritance pattern
Farber's disease	Lysosomal storage diseases	Paralysis of the arms and legs (quadriplegia), seizures, loss of speech, involuntary muscle jerks (myoclonus), and developmental delay	Autosomal recessive
Krabbe's disease	Lysosomal storage diseases	Irritability, muscle weakness, feeding difficulties, episodes of fever without any sign of infection, stiff posture, and slowed mental and physical development, vision loss and seizures	Autosomal recessive
Tay-Sachs disease	Lysosomal storage diseases	Loss of motor skills such as turning over, sitting, and crawling exaggerated startle reaction to loud noises, seizures, vision and hearing loss, intellectual disability, and paralysis	Autosomal recessive

(continued)

Table 11.2 (continued)

Neurodegenerative disorder	System involved	Neurologic/psychiatric/behavioral abnormalities	Inheritance pattern
Alexander disease	Leukodystrophies	Megalencephaly, seizures, spasticity, intellectual disability and developmental delay	Autosomal dominant
Canavan disease	Leukodystrophies	Feeding and swallowing difficulties, seizures, and sleep disturbances, developmental delay, hypotonia, macrocephaly, abnormal posture, and intellectual disability	Autosomal recessive
Pelizaeus-Merzbacher disease	Leukodystrophies	Impaired intellectual functions, such as language and memory, delayed motor skills, such as coordination and walking	X linked recessive
Leigh disease	Mitochondrial disease	Hypotonia, involuntary muscle contractions (dystonia), ataxia, peripheral neuropathy, weakness or paralysis of the muscles that move the eyes (ophthalmoparesis); rapid, involuntary eye movements (nystagmus); or degeneration of the nerves that carry information from the eyes to the brain (optic atrophy), severe breathing problems, and hypertrophic cardiomyopathy	Autosomal recessive/X linked recessive/ Sporadic
Medium-chain acyl CoA dehydrogenase deficiency	Mitochondrial disease	Lethargy, vomiting, seizures, breathing difficulties, liver problems, coma, and hypoglycemia	Autosomal recessive
Phenylketonuria	Amino acids and organic acid diseases	Profound intellectual disability, developmental delay, microcephaly, seizures (e.g., tonic-clonic, myoclonic, infantile spasms), tremors, athetosis, and spasticity, autistic behavior and attention-deficit–hyperactivity disorder	Autosomal recessive
Glutaric aciduria type I	Amino acids and organic acid diseases	Macrocephaly, muscular spasms, jerking, rigidity, or decreased muscle tone	Autosomal recessive
Lowe syndrome	Central nervous system and eyes and kidneys	Delayed development, impaired vision, moderate to severe intellectual disability, Kidney abnormalities, seizures, weak muscle tone from birth (neonatal hypotonia), feeding difficulties and problems with breathing	X linked recessive
Biotinidase deficiency	Enzymes that depend on Vitamin biotin	Seizures, weak muscle tone (hypotonia), breathing problems, and delayed development, hearing loss, eye abnormalities, loss of vision, problems with movement and balance (ataxia), skin rashes, hair loss (alopecia)	Autosomal recessive

Table 11.3 Some neurodegenerative disorders in childhood and adolescence showing the principal systems affected, neurologic/psychiatric/behavioral abnormalities and their inheritance patterns

Neurodegenerative disorder	System involved	Neurologic/psychiatric/behavioral abnormalities	Inheritance pattern
Charcot Marie tooth disease	Peripheral nerves	Balance difficulties, clumsiness, and muscle weakness in the feet, loss of sensation and wasting (atrophy) of muscles in the feet, legs, and hands	Autosomal dominant
Wolfram syndrome (diabetes insipidus, diabetes mellitus, optic atrophy and deafness) [DIDMOAD]	Multisystem	Depression, paranoia, auditory or visual hallucinations, violent behavior, dementia, suicide	Autosomal recessive
Symptomatic progressive myoclonic epilepsies (such as Unverricht-Lundborg disease (ULD) and Lafora disease)	Central nervous system and for Lafora disease in addition-affects heart, liver and muscle	Myoclonic jerks and tonic-clonic seizures visual hallucinations (occipital seizures), progressive neurologic degeneration including cognitive and/or behavioral deterioration, dysarthria, and ataxia	Autosomal recessive
Metachromatic leukodystrophy	Central and peripheral nervous system	Anxiety, depression, emotional lability, social withdrawal, schizophrenia, poor memory	Autosomal recessive
Late-onset GM2 gangliosidosis	Lysosomal disorder	Dystonia, intention tremor, dementia, obsessional paranoia, hallucinations, acute psychosis, dysarthria	Autosomal recessive
Juvenile Huntington's disease	Basal ganglia	Rapid, significant drop in overall school performance, depression, gait disturbances, tremors or slight involuntary movements, seizures, obsessive compulsive disorder, mania, sexual inhibition or inappropriate sexual behaviours	Autosomal dominant
Fabry's disease	Lysosomal storage disorder	Pain, particularly in the hands and feet (acroparesthesias); a decreased ability to sweat (hypohidrosis); cloudiness of the front part of the eye (corneal opacity); ringing in the ears (tinnitus); and hearing loss	X-linked recessive
Kearns-Sayre syndrome	Mitochondrial disease	Cardiac conduction defects, ataxia, muscle weakness, deafness, kidney problems, and a deterioration of cognitive functions (dementia)	Variable
MELAS syndrome, NARP	Mitochondrial disease	Recurrent stroke-like episodes in the brain, migraine-type headaches, vomiting and seizures, general muscle weakness, exercise intolerance, hearing loss	Variable

(continued)

Table 11.3 (continued)

Neurodegenerative disorder	System involved	Neurologic/psychiatric/behavioral abnormalities	Inheritance pattern
MERRF syndrome	Mitochondrial disease	Myoclonus (muscle jerks), seizures, ataxia, muscle weakness, hearing impairment	Variable
Juvenile neuronal ceroid lipofuscinosis	Lysosomal storage disorder	Inappropriate behavior, thought disorder, paranoia with hallucinations, delusions	Autosomal recessive
Subacute sclerosing panencephalitis	Central nervous system	Deterioration in learning or schoolwork, involuntary movements, deterioration in the thought processes, myoclonic jerks, epileptic seizures may or may not occur	Sporadic
Adrenoleukodystrophy	Central nervous system and the adrenal glands	Difficulty reading or writing, obsessional behavior, irritability, social withdrawal, dementia	X-linked recessive
Variant Creutzfeldt–Jakob disease	Central nervous system	Dementia, blurred vision, gait changes, disorientation, hallucinations, lack of coordination, myoclonic jerks or seizures, personality changes, sleepiness, speech impairment	Unknown
Wilson disease	Multisystem especially liver, brain, and eyes	Antisocial behavior, anxiety, depression, manic depressive psychosis, clumsiness, tremors, difficulty walking and mood swings	Autosomal recessive
Multiple sclerosis	Central and peripheral nervous system	Overwhelming fatigue, visual disturbances, altered sensation and difficulties with mobility, muscle stiffness (spasticity), exaggerated reflexes (hyperreflexia), or poor bladder control	Unknown
Friederich's ataxia	Central and peripheral nervous system -spinocerebellar degeneration	Ataxia, gradual loss of strength and sensation in the arms and legs, muscle stiffness (spasticity), impaired speech, hypertrophic cardiomyopathy, impaired vision, hearing loss, or an abnormal curvature of the spine (scoliosis)	Autosomal recessive
Gaucher's disease type III	Lysosomal storage disorder	Hepatosplenomegaly, Anemia, Thrombocytopenia, Bone disease (bone pain and fractures), seizures and slowing of horizontal eye movements	Autosomal recessive

Regression and Progressive Neurological Deterioration Are Cardinal Features

The presentation of a child with a neurodegenerative developmental disorder has varied manifestations. Some children may present with a history of regression in previously acquired developmental milestones, or history of a delay in acquisition of milestones, history of no further attainment of milestones following previously normal progress or a history of total loss of previously acquired milestones. This is graphically illustrated in Fig. 11.1 that demonstrates the possible developmental trajectories of child development. Child (A) depicts the normally developing child who attains the neurodevelopmental milestones at the appropriate successive age. Child (B) shows a child having a fairly stable developmental progress however this is made at twice the successive age and is a picture typical of children with cognitive impairment. Child (C) shows an initial developmental progress which then levels off with hardly any more variation. This represents a child with a neurodegenerative disorder even in the absence of developmental regression. Child (D) initially exhibits a similar trend as is seen in child (C) nonetheless this is followed by gradual loss of developmental skills and is a picture that typifies "classic" neurodegenerative disorder. Child (E) on the other hand shows that this gradual loss of skills is not necessarily a smooth uninterrupted process but may proceed in intermittent bursts of deficits which may denote stress arising from the effects of injury or illness.

In certain circumstances it can be challenging to differentiate between a plateauing of skills, a pseudo-regression and real onset of a neurodegenerative condition in a child with a pre-existing neurological deficit. In such situations it is important to review the authenticity of the original diagnosis and institute the appropriate measures where possible to reverse the condition. Some causes of pseudo-regression

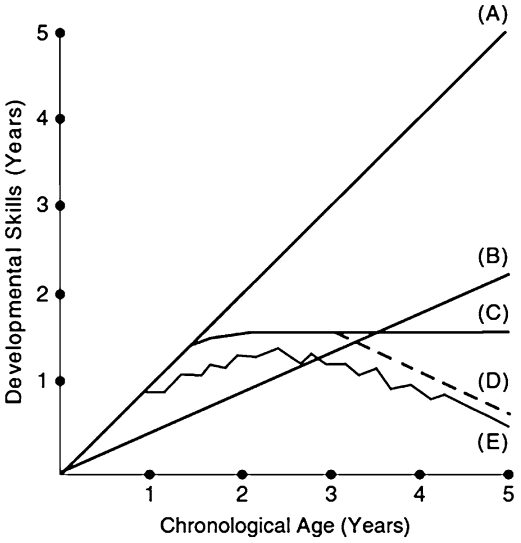

Fig. 11.1 Graphic representation of childhood development (Reproduced with permission from Goldstein E. M, & Holden K.R, (2009), Neurodegenerative Disorders: Variable Clinical Presentation of Cognitive Decline, in Bernard L. Maria (ed.), Current Management in Child Neurology (4th Edition, pp. 322–336), Shelton, CT: People's Medical Publishing House, (PMPH-USA))

may include: depression especially in adolescents, poorly controlled and subtle epileptic seizures as is seen in unrecognized absence seizures or non-convulsive ("subclinical") status epilepticus, acquired hypothyroidism, substance abuse, lead encephalopathy, repeated traumatic brain injury and in children deprived of emotional contact as seen in prolonged hospitalizations [13] or in those who witness domestic violence [14].

Initial Evaluation of Children Suspected of Suffering from Neurodegenerative Disorders

A comprehensive history taking followed by detailed physical examination is paramount when evaluating children with suspected neurodegenerative disorders [4, 12, 15]. A thorough history taking is essential for the assessment of any child with developmental regression in order to exclude other disorders that may mimic neurodegenerative disorders. Following an uneventful pregnancy and delivery of a normal full term child, the child with suspected neurodegenerative disorder may either present with an acute and rapidly progressive or a vague and slowly progressive course. For the latter course it is crucial that it should be distinguished from a static non-progressive disorder. The slowly progressive course primarily affects the white matter and can commence in infancy, childhood or adolescence. Usually the acute onset predominantly affects the gray matter and is seen in neonatal or early infancy with the symptoms commencing a few days after birth.

Following an in-depth history, a formulation of differential diagnoses is made to come to a diagnostic hypothesis directing subsequent laboratory investigations. A classic distinction in the group of neurodegenerative disorders involves those with predominant white matter involvement (such as Multiple Sclerosis, Adrenoleucodystrophy, Alexander Disease, Canavan Disease, Krabbe Leukodystrophy, Metachromatic Leucodystrophy) versus those with predominant gray matter involvement (such as Mitochondrial Encephalopathies, Neuronal Ceroid Lipofuscinonis, Progressive Infantile Poliodystrophy, and the Symptomatic Progressive Myoclonic Epilepsies) [16].

White matter disorders typically feature onset in late childhood, with initially normal cognitive functions, but early and prominent spasticity and cerebellar signs, gait difficulties, and early peripheral neuropathy due to demyelination. Later signs occasionally include focal neurologic deficits, seizures and megalencephaly. Other signs are absence of exaggerated reflexes and optic atrophy. The electroencephalogram (EEG) shows diffuse delta slowing, the electromyogram (EMG) shows slowed nerve conduction velocity and evoked potentials are prolonged or absent.

Disorders primarily affecting white matter can be subdivided into two broad categories, demyelinating and dysmyelinating/hypomyelinating. Demyelination occurs when immune-mediated inflammatory responses, toxic exposure, or vascular injury destroys previously normal myelin, as for example in multiple sclerosis, acute disseminated encephalomyelitis, acute hemorrhagic leukoencephalitis and

myelinoclastic diffuse sclerosis of Schilder. These white matter disorders likely have an immunological basis but their mechanisms are not completely understood. Disorders that involve dysmyelination or hypomyelination include metabolic diseases affecting the nervous system such as galactosemia, pyridoxine-dependent seizures, infantile Refsum's Disease, metabolic disorders of lipid metabolism (e.g., Metachromatic Leukodystrophy, Krabbe's Disease, and diseases affecting myelin proteins (e.g., Pelizaeus-Merzbacher) (see Tables 11.1, 11.2, and 11.3).

In contrast, gray matter disorders manifest typically in early infancy with microcephaly, early severe seizures, and progressive dementia. Later features are axonal loss, retinal degeneration, progressive spasticity. The reflexes remain normal or become exaggerated. The EEG shows epileptiform discharges, the EMG and evoked potentials are usually normal. The main localization of grey matter loss is specific in some disorders. The basal ganglia are mainly involved in Juvenile Huntington Disease or Wilson Disease. Friedreich Ataxia involves spinocerebellar degeneration; in Spinal Muscular Atrophy, a genetic defect causes targeted death of neuronal cells in the anterior horn of the spinal cord with subsequent system-wide muscle wasting (see Tables 11.1, 11.2, and 11.3).

It is conceded that many neurodegenerative disorders have mixed white and gray matter involvement, or both grey and white matters are involved in a later stage of many of the disorders. Classification schemes may use the type of underlying molecular and genetic defect and change as such due to advances in identifying these defects. Examples are the group of Peroxisomal Disorders that include Adrenoleucodystrophy and Zellweger Syndrome, and the group of Lysosomal Disorders including Krabbe Leukodystrophy and Metachromatic Leukodystrophy).

Postnatal complications such as kernicterus, sepsis, meningitis, and head trauma should be investigated in the history as non-supportive of a neurodegenerative disorders. On the other hand, a positive family history of neurological disorders or early and unexplained deaths may suggest the presence of an undiagnosed inherited neurodegenerative disorder. Other confounders mimicking neurological regression and deterioration such as medical disorders, visual impairment, hearing loss, epilepsy, autism spectrum disorders, intellectual disability, attention-deficit hyperactivity disorders, or child abuse and neglect need to be considered when taking the history.

The clinical examination should include head circumference to detect megalencephaly, an important feature in Canavan, Tay-Sach's, Sandhoff's and Alexander Disease, or microcephaly that is a usual feature of many gray matter disorders due to progressive neuronal loss. Dysmorphic features need to be assessed as facial dysmorphisms are associated with some neurodegenerative disorders such as Zellweger Syndrome and mucopolysaccaridoses. A thorough neurological examination permits us to further define which specific nervous system functions or systems are deranged. In particular one should also assess ocular abnormalities that are prevalent in neurodegenerative disorders, in the form of optic atrophy in white matter disorders and retinal degeneration in grey matter disorders.

More specifically during the eye examination, look out for evidence of cortical blindness as in MELAS syndrome, abnormal movements (as in Ataxia telangiectasia,

Gaucher's disease, types 2 and 3, Kearns-Sayre syndrome and Pelizaeus-Merzbacher disease), corneal clouding (as in Wilson's disease and Hurler's disease), lens opacities (as in Fabry's disease, Galactosemia, Lowe syndrome,) optic atrophy (as in Canavan disease Metachromatic leukodystrophy, Adrenoleukodystrophy and Pelizaeus-Merzbacher disease) or a Cherry Red Macula (as seen GM1 gangliosidosis, Tay-Sachs disease, Sialidosis type I).

Specific clinical findings give clues to the diagnosis. For example, hepatomegaly and/or splenomegaly are prominent in mucopolysaccaridosis, sphingolipidosis, peroxisomal and mitochondrial disorders. Progressive renal failure is found in Fabry Disease and Lowe Syndrome. Abnormalities of the hair (seen in Menkes syndrome, Biotinidase deficiency and mucopolysaccaridoses), the kidneys (as in Zellweger syndrome). Mucopolysaccaridosis, Friedreich Ataxia, and mitochondrial disorders are associated with cardiac disorder.

Investigations for Neurodegenerative Disorders

As a general rule, findings on history and physical examination should guide the selection of laboratory investigations as many neurodegenerative disorders have unique genetic, metabolic, or enzymatic markers. Facilities for a comprehensive workup for most neurodegenerative disorders are currently unavailable in Uganda with most assays having to be performed by overseas laboratories.

Initial laboratory studies should include blood analysis covering complete blood count, glucose, calcium, anion gap, electrolytes, renal function tests, ammonia, aminotransferases, lactic acid, pyruvic acid, uric acid and ketones. Urine analysis is done for ketones, pH, aminoaciduria, organic aciduria, homocystinuria, mycopolysaccharides and oligosaccharides. Serum ammonia, lactate, pyruvate, amino acids, and urine for amino acids and organic acids would screen for most amino acids disorders, organic acidopathies, and urea cycle abnormalities. Chest X-ray may show cardiomegaly in mitochondrial disorders, Friedreich Ataxia, and mucopolysaccharidosis. Conduction abnormalities may be present on electrocardiogram (ECG). Skeletal survey may reveal specific bony abnormalities such as dysostosis multiplex in mucopolysaccharidosis.

Children with dysmorphic features should have genotyping and chromosomal studies. Other investigations that bring important information are EEG often showing bilaterally synchronous paroxysmal discharges in grey matter disorders versus continuous non-paroxysmal slow wave activity in white matter disease. In diseases involving both the grey and white matter, the pattern may be mixed with both bilaterally synchronous paroxysmal discharges and markedly increased recordings of slow wave activity. The electroretinogram (ERG) may provide information about retinal involvement that features in several metabolic diseases. Recording of visual evoked potentials assist in documenting retinal lesions that may be more focal or restricted to retinal ganglion cells as in gangliosidosis. Brainstem auditory evoked potentials may be abnormal in a demyelinating disease or in axonal lesions. Nerve

conduction studies show decreased nerve conduction velocity in demyelinating neuropathy, and decreased amplitude of the motor or sensory action potential in axonal neuropathy. Abnormal neurogenic changes can be differentiated from myopathic changes by analysis of the electromyogram.

Specific diagnostic tests and enzyme assays can be done to identify specific neurodegenerative disorders that often involve skin fibroblast culture, CSF examination, DNA studies, nerve, or muscle biopsies. These tests are not done routinely but only in specialized laboratory, are often expensive, and can be found in other literature [17].

Role of Neuroimaging

There are a range of neuroimaging techniques that could be employed for the early diagnosis of neurodegenerative disorders; however one needs to consider the purpose of the investigation. Early diagnosis may be used to appropriately delineate a specific disease condition from others that may present with similar clinical symptoms especially in the early stages, alternatively it may be utilized to timely identify a malfunctioning central nervous system before the clinical symptoms appear.

In Uganda there are limited diagnostic modalities with respect to brain imaging despite its significant value. Cranial computed tomography (cranial CT) and magnetic resonance imaging (MRI) brain scans are usually employed. MRI however plays a primarily vital role in diagnosis of central nervous system degenerative illnesses because it is exceptional in the visualization of many cerebral abnormalities compared to CT.

Other powerful neuroimaging techniques that permit visualization of organ structure and function with precision include: positron emission tomography (PET) and single photon emission computed tomography (SPECT) but these are currently unavailable. These utilize radio-ligands which measure in detail the functioning of distinct areas of the human brain and are beneficial in detecting and characterizing potential pathophysiological brain changes. These methods particularly PET that has the higher sensitivity are of great value in detecting early stages of the causes of cognitive impairment [18].

General Treatment Guidelines

Treatment can be directed towards the underlying disorder, associated features, and complications. Dietary restriction is useful in certain diseases such as phenylketonuria, maple syrup urine disease, adrenoleukodystrophy etc. Treatable complications include epilepsy, sleep disorder, behavioral problems, feeding difficulties, gastroesophageal reflux, spasticity, drooling, skeletal deformities, and recurrent chest infections. Specific treatments to counteract the offending metabolite (s), improve

or decrease abnormal enzyme function, or to off-set metabolic dysfunction are possible for specific diseases in addition to organ transplantation including bone marrow transplantation (when irreparable brain damage has not occurred). Bone marrow transplantation has been shown variable but promising results in lysosomal storage diseases, mucopolysaccharidoses, Gaucher's Disease, metachromatic leukodystrophy, and adrenoleukodystropy. It may be possible in the future to target specific pathways with somatic gene therapy but this will require more technological advances and discoveries. A referral for genetic counseling is important due to heritability of many neurodegenerative disorders. Public health initiatives should focus on the risk of consanguineous marriages as a way to raise awareness of a preventable cause of neurodegenerative disorders in childhood.

Common Etiologies of NDDD's Seen in Uganda

Human Immunodeficiency Virus (HIV)

The human immunodeficiency virus (HIV) belongs to the Lentivirus genus of the Retroviridae family. The UN estimates that there were 35.3 (32.2–38.8) million people in the world infected with HIV in 2012 [19]. Uganda is estimated to have 1.5 million people living with HIV-1, of whom 190,000 are children [20].

HIV-1 is the most common cause of HIV infection in Africa with mother-to-child transmission of HIV (MTCT) being the major mode of acquisition of infection in children. The estimated risk of perinatal acquisition of untreated women to their infants ranges from 13 % to 30 % with approximately 400,000 new HIV-1 infections occurring each year [20].

A very high mortality is seen in low income countries with mortality rates of over 50 % by the age of 2 years when no treatment is instituted [21] and Uganda is no exception [22].

The HIV virus has a predilection for the Central Nervous system especially the microglia with as many as 10 % of children with AIDS developing HIV progressive encephalopathy (HPE). Information from a systematic review of studies on paediatric HIV/AIDS and neurodevelopment in infancy in Sub-Saharan Africa (SSA) shows that HIV affects all spheres of child functioning. The sphere of motor development is the most noticeably affected in terms of severity, time of onset and persistence across the age groups [23]. The cognitive sphere is also significantly affected compared to their age and gender matched HIV negative peers. One study found that despite being clinically and neurologically stable, school-aged HIV- positive children (aged 6–11 years) had considerably lower cognitive scores compared with the age and gender-matched HIV negative children [24].

In contrast, an earlier long-term prospective study of HIV-infected Ugandan children followed from birth to school age, found no evidence of significant differences in neurologic, motor, and psychometric development when compared with seroreverter children or with HIV negative children who were born to HIV-negative mothers.

This was attributed to possible earlier death of the severely ill children with HIV encephalopathy in the cohort leaving survivors with a somewhat static/stable expression of the disease hence the normal range cognitive assessments [25].

Risk Factors

The timing of HIV infection is the risk factor identified so far as contributory to this condition, with significantly lower cognitive function scores noted in children testing positive in the first 3 weeks of life compared to the scores of those identified later than this [26].

Other identified risk factors based on studies also done in adults include:

- Host factors- genetic predisposition, low educational status, presence of metabolic disorders, co-infection with hepatitis C virus and IV drug abuse.
- Viral factors- the virus subtypes B, C, D and F more related than subtype A [27–29].
- Relation of host and virus- an advanced stage of HIV/AIDS, low level of CD4+ counts, presence of chronic immune activation manifesting by increased levels of cytokines, interleukins and other serum markers. e.g. monocyte chemoattractant protein 1 (MCP-1), TNF-alpha, hsCRP, raised level of HIV-DNA load in circulating macrophages and higher CSF viral load compared to serum viral load [30, 31].

Clinical Features

HIV-associated progressive encephalopathy (HPE) is a syndrome complex characterized by a triad of cognitive, motor, and behavioral features similar to features of "AIDS dementia complex (ADC)" seen in adults [32, 33].

HPE affects children in a variable, non-linear course, however three definite patterns are identified [34, 35]:

(i) The rapid progressor group,
(ii) The sub-acute (slow) group
(iii) The static neurological group.

Similarly to adult patients, HPE may occur in children in the absence of HIV opportunistic infections or with malignancies of the central nervous system. Children may present with developmental regression, behavioral disorders, microcephaly or cerebellar signs.

Pathogenesis

The pathogenesis of HIV related central nervous system (CNS) involvement is not well understood. It is however postulated that during the early course of the infection [36], HIV enters the CNS via the CD4 T lymphocytes and monocytes, which

cross the blood-brain barrier (BBB). The infected monocytes convert into perivascular macrophages in the nervous tissue, as the HIV virus spreads to infect the local macrophages (microglia). The perivascular macrophages and microglia merge to form multinucleated giant cells (MGCs). These MGCs serve as HIV reservoirs by replicating the virus and producing neurotoxic viral molecules: viral (gp-120 and tat protein) [37]. These neurotoxins activate astrocytes, which in turn release cytokines and cause BBB breakdown enhancing the movement of more HIV-infected cells from blood to brain. In addition the astrocytes damage the neurons, resulting in demyelination and neuronal loss.

Diagnosis

According to the Consensus of Pediatric Neurology/Psychology Working Group, AIDS Clinical Trial 1996, [38] a definitive diagnosis of HPE requires at least one of the options below to be present for at least 2 months in the absence of a coexisting illness other than HIV infection:

1. Failure to achieve or loss of developmental milestones, or a loss of intellectual ability, verified by normed developmental scales or neuropsychological tests;
2. Poor brain growth, or acquired microcephaly validated by head circumference measurement, or brain atrophy demonstrated with neuro-imaging with CT or MRI scans with serial imaging necessary in children less than 2 years of age; and
3. Acquired symmetric motor deficits exhibited as: hyperreflexia and/or pathologic reflexes, hypertonia, paralysis or gait disturbances.

Unlike typical neurodegenerative syndromes there is a variable degree of reversibility for HPE. Highly Active Antiretroviral Therapy (HAART) has been shown to retard/or possibly reverse the progress of HIV-associated encephalopathy [39]. However, despite the clinical stability and use of anti-retroviral medications, there is still ongoing cognitive decline mostly attributable to the HIV infection implying that HAART may not completely reverse established encephalopathy in all cases [40].

Cerebral Malaria

Malaria is an important parasitic infestation in humans with four species responsible for producing the illness. i.e. *P. vivax, P. ovale, P. malariae* and *P. falciparum*. Infection with *Plasmodium falciparum* is responsible for the severe and complicated manifestations and in children presents with a varied spectrum of signs, symptoms, and history. This ranges from a life threatening disease to an apparently asymptomatic infection, from a rapidly progressing, fulminant illness to a chronic insult. The most severe neurological complication of *P. falciparum* malaria is cerebral malaria and has been associated with case-fatality rates of 10–40 % in hospital-based studies [41].

Clinical Features

In children cerebral malaria presents with fever, seizures, coma, and brainstem signs. The characteristic feature of cerebral malaria is impaired consciousness, with coma as the most severe manifestation which may be of gradual or sudden onset. Furthermore seizures, brain oedema, retinal changes (papilledema, haemorrhages, peripheral and macular whitening) and brainstem signs (irregularities in pupil size and reaction, abnormal eye movements, abnormalities in posture and respiratory patterns) may be manifested. Some children develop life-threatening complications such as severe anaemia, electrolyte imbalance, metabolic acidosis, hyperpyrexia, hypoglycemia, shock, or encephalopathy [42].

Risk Factors

Among some of the identified risk factors associated with development of Cerebral Malaria include [43–46]:

- Child factors- such as being of an age above 2 years, higher level of parisiteamia, having a higher number of siblings (>4), presence of malnutrition, having HIV type 1 infection, initial treatment in clinics, late presentation/consultation, non-use of mosquito nets, presence of fresh abdominal scarification and presence of genetic host factors host genes including Transforming Growth Factor Beta 2 (TGFB2) and Heme oxygenase-1 (HMOX1).
- Socio-economic factors- such as low social economic class of the family, non-living together of parents, or poor access to health facilities.
- Parental factors- such as young mother, or low level of maternal education.

While an apparent full recovery is observed in more than 85 % of children who recover from cerebral malaria [41], approximately 25 % have persistent neurological sequelae such as seizures, cortical blindness, ataxia or generalized spasticity. Others survive with concealed effects such as defects in learning, behaviour, or cognition [42, 47, 48].

Pathogenesis

The pathophysiology for these clinical features results from cerebral malaria causing a disseminated vasculomyelinopathy. This results in the histopathologic changes in the brain that include: edema, neuronal degeneration, perivascular infiltrates, perivascular demyelination, ring hemorrhages, and the microglial-astroglial nodules (Dürck's granulomas) in the late stages [49, 50]. Furthermore, the high temperatures contribute to degeneration of the neurons in the cortex, cerebellum and basal ganglia [51].

Diagnosis

Usually the diagnosis of cerebral malaria is made from a suggestive history, clinical features and a positive blood smear (on microscopy). In the absence of a positive blood smear the alternative use of rapid tests such as the immunochromatographic test for P. falciparum histidine-rich protein 2 and lactate dehydrogenase or Polymerase chain reaction tests may be used however their sensitivity and specificity plus inability to estimate the parasite load are impediments [52, 53]. Based on findings from a Malawian postmortem study, the presence of Malarial retinopathy showed increased specificity in distinguishing patients with features of Cerebral Malaria from other encephalopathies. Cerebral spinal fluid (CSF) analysis usually shows mild pleocytosis and an increase in protein. Raised levels of CSF and Blood levels of lactate may be observed. Neuroimaging typically shows brain oedema [54].

Measles

Measles is an acute viral illness caused by a morbillivirus of the paramyxovirus family. Measles continues to be an endemic illness in Uganda, despite efforts to control the outbreaks through mass measles vaccination campaigns. The impact of these campaigns is usually short-lived, not lasting more than 2 years [55]. Currently less than half of the children in Uganda receive complete immunization [56]. The majority of all measles cases (93 %) and of severe cases (97 %) are among children <15 years of age [57].

Approximately three in every ten cases of measles have one or more complications. These complications are more common in children under 5 years of age with higher mortality rates observed in the immunocompromised, the malnourished and in those with vitamin A deficiency. Among the neurological complications include: convulsions (0.5 %) and encephalitis (0.1 %).

Clinical Features

Subacute sclerosing panencephalitis (SSPE) is one of the three types of measles encephalitis (the other two being acute demyelinating encephalomyelitis and measles inclusion body encephalitis).

SSPE is a neurodegenerative disease resulting from a post infectious neurologic complication of measles. A persistent infection of the brain caused by an altered form of the measles virus is implicated in the pathophysiology. The prevalence of SSPE is dependent on how successful the measles vaccination coverage was, with the higher incidence in areas having low vaccination rates. The mechanisms underlying the viral persistence and the trigger of the viral reactivation remain elusive.

It is however suspected that as a result of genetic polymorphism, those individuals who develop SSPE exhibit an altered cellular response to the measles antigen. This results in premature production of antibodies following measles infection that impairs the host's immune cells' ability to eliminate the virus and, thus, supports a chronic intracellular infection [58–60].

In most instances following an acute measles infection, the infected children remain symptom-free for 6–15 years [61]. The risk is higher in those acquiring measles before the second birthday [62]; with the risk of SSPE being 16 times greater when it occurs in children less than 1 year of age than in those over 5 years of age [63]. The prevalence of SSPE is notably more in males than females with the onset of symptoms later in the latter group as well [64, 65].

Risk Factors

Among the risk factors associated with SSPE include [66–68]:

- Child factors- such as being of a higher birth order, younger age at measles onset, having a higher number of siblings or having HIV/AIDS.
- Socio-economic factors- such as living in poverty, congested homes, or in rural areas.
- Parental factors- such as an older mother, mother with HIV/AIDS or low level of parental education.

The initial symptoms of SSPE usually present 6 years after measles infection. The affected individuals present with progressive cognitive and intellectual deterioration that may manifest in poor school performance, personality changes, and behavior abnormalities. A period of continual motor decline ensues and over a series of months, the psychological symptoms are complicated by neurologic ones that include: myoclonic jerks, focal weakness, autonomic malfunction, seizures and rigidity, finally leading to death with akinetic mutism [65, 69, 70].

Pathogenesis

The pathophysiology for these clinical features results from oedema, principally seen in the early course of this disease. Infected cells show DNA and ribonucleic acid oxidative damage coupled with lipid peroxidation in areas exhibiting early demyelination. As the disease progresses there is cortical and subcortical perivascular infiltration of inflammatory cells, spongiosis, and demyelination in the acute phase, followed by neuronal loss. In the preliminary stages, the posterior areas of the brain are the most affected, followed by spread to the anterior regions with limited involvement of the cerebellum [71].

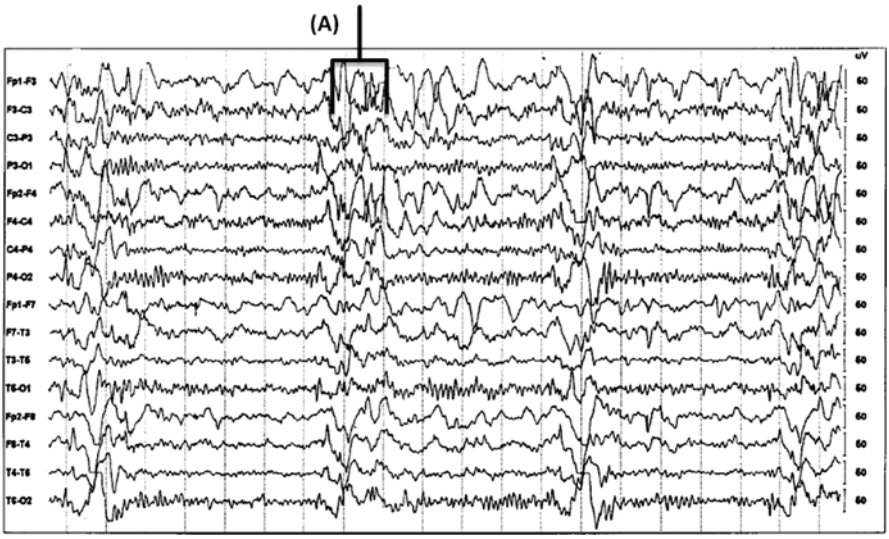

Fig. 11.2 An electroencephalogram showing a "burst-suppression" pattern highly characteristic of subacute sclerosing panencephalitis (SSPE). An example of runs of periodic bursts of high-amplitude, slow-wave complexes with a normal background rhythm apart from bifrontal slowing is shown in (*A*)

Diagnosis

The diagnosis of SSPE is accompanied by a unique set of laboratory abnormalities that facilitate its diagnosis which include: CSF analysis which shows normal cellular components, glucose and total protein, but grossly elevated values of gamma globulins and serum anti-measles antibodies. In almost all cases, the EEG reveals a "burst suppression" pattern at some point in the course of SSPE as shown in Fig. 11.2. The bursts of abnormal sharp and slow waves typically arise out of a normal background EEG activity early in the course of SSPE, but this background activity deteriorates to diffuse slow waves as the disease progresses [61].

The brain MRI may initially be normal, or may show focal abnormalities in the subcortical white matter with posterior cortico-subcortico lesions on diffusion weighted imaging (DWI) [72]. Later, diffuse cerebral atrophy, periventricular white mater T2 hyper intensities and basal ganglia are classically described [73]. A combination of the clinical features with supportive EEG and radiological findings should lead one to suspect a diagnosis of SSPE.

Nodding Syndrome

Nodding syndrome (NS) is a puzzling, often progressive, disorder that has been described in African children [74, 75]. Uganda [74, 76] is one of four African countries that have reported cases of this condition among its populations, with initial

reports coming from Tanzania [77] and subsequently Liberia [78] and South Sudan [79–81]. The northern region of the country constitutes the major area where these cases are found with the first cases reported around 1997 and peaking at the height of the political insurgency that afflicted this region for more than 20 years from 1986 and when people moved into protected Internally Displaced Peoples (IDP) camps (MOH, report). To date an estimated total of over 10,000 cases have been identified in children and adolescents from South Sudan, United Republic of Tanzania and Uganda [82]. The true burden of the syndrome in Uganda is unknown. It is currently not known if NS is a true neurodegenerative disorder due to lack of research and knowledge about etiology and mechanism. Anecdotal reports describing a down ward trend of progressive neurologic deterioration, psychiatric symptoms, physical wasting and ultimately death. Deaths from drowning/burning accidents, opportunistic infections, self-injury, persistent seizure episodes have been reported by the caregivers [84]. Whereas symptomatic improvement has been noted to occur in children with NS given nutritional and vitamin supplementation, antidepressants and/or anticonvulsants [83], no child is known to have completely recovered from nodding syndrome, and the long-term outcomes of the illness are still poorly understood [84]. It has been noted that there is parallel relationship between the nutritional status of patients with NS and the degree of severity of wasting and stunting observed in the children and the length of duration of symptoms, being most marked in those having symptoms with a longer duration [85].

Clinical Features

From the clinical descriptions of Nodding syndrome in the literature, children initially get afflicted, between the ages of 3 and 18 years (MOH report), with the 6–11 years age group being more frequently affected [86]. The children are noted to develop bouts of repetitive dropping forward of the head, termed “head nods” which are atonic seizures [74]. The head nodding is often accompanied by other seizure types such as generalized tonic-clonic, myoclonic, complex partial and absence seizures [74, 85]. Precipitants of these “head nods” include the sight of food, taste of a hot meal or cold drink [74], presence of cold weather or bathing in cold water [87] while in others no specific precipitant has been identified [85].

The head nods often precede the other seizure types by 2–4 years and continue together in some case while in others the head nods cease and the other seizures types take over.

While documented natural history studies are lacking, over the course of time following progressive brain damage, the children acquire cognitive, motor, and behavioral impairments with subsequent malnutrition and growth retardation. Focal neurological deficits are rare. There is a decline in school performance followed by eventual school drop-out [74, 85, 87]. Other reports document aggressive behavior, self-injurious outbursts, depression, visual hallucinations, loss of speech/slurred speech, upper and lower limb disfigurements with chest and vertebral bone deformities [84, 85]. A delayed sexual maturity with delayed bone growth has also been

documented [84]. NS patients also exhibit several catatonic symptoms including: slowing of movements, immobility alternating with purposeless agitation, muteness, repetitive movements, staring, posturing, grimacing, social withdrawal, negativism (including active or passive refusal to eat and drink), and urinary incontinence [83–85]. In a pilot study conducted in one of the Northern districts in Pader to determine whether NS patients meet clinical criteria for pediatric catatonia and their response to a catatonia test using lorazepam, the first-line treatment for catatonia, many of these clinical features were confirmed as well as the safety and possible benefits of Lorazepam in the treatment of NS required larger and controlled follow-up studies (Kakooza 2014, in preparation).

Pathogenesis

Regardless of previous investigations, the cause of the syndrome and the pathogenesis remain indeterminate. Possible postulations include:

- A degenerative brain disorder complicated with seizures. The origin of the degeneration could be from poorly treated infections like viral encephalitis, cerebral malaria, *O. volvulus* or traumatic brain injury resulting into repeated seizures with subsequent cognitive decline. The association with *O. volvulus* however is considered by some to be false [79, 81, 84, 86]. In addition, the screening for several viral central nervous system infections using PCR, for a possible etiological agent have proven futile [88]. Mass treatment of NS with Ivermectin and anticonvulsants, however did not control NS [84].
- An epidemiological study conducted by the Ugandan Ministry of Health and the US Centers of Disease Control found most cases and controls had low vitamin B6 levels [88], nursing the possibility that vitamin B6 deficiency may be contributory to disease pathogenesis. Since vitamin B6 is an important factor in the synthesis of neurotransmitters, any reduced levels could lead to impaired neurologic function with possible intractable seizures, the so called pyridoxine dependence seizures [89, 90]. Treatment with pyridoxine, however, did not control NS.
- Severe psychological trauma following chronic and repeated war- traumatization (both direct and indirect) in the children resulting in severe chronic Post-Traumatic Stress Disorder, coined "Developmental Trauma Disorder" (DTD) [84, 91] has been suggested. This could be complicated by chronic depression and anxiety or catatonia [92, 93] and lead to poor appetite or food refusal resulting in severe malnutrition [84].

Other etiological considerations have included depression with or without conversion symptoms, slow virus infection or prion disease, a newly discovered mitochondrial disease, neuro- toxic brain injury, chronic inflammatory brain diseases, or a mutant genetic disorder. Others have entertained that it could be as a result of a combination of any one of the previously mentioned possibilities. There is need for future multicenter studies in Uganda and other affected sites to explore possible causes/risk factors for NS and their role in this enigmatic condition.

Conclusion

Neurodegenerative disorders, although individually rare, encompass a large heterogeneous group of disorders that stem from specific genetic and biochemical defects, chronic viral infections and varied unknown causes. Comprehensive history taking followed by detailed physical examination is paramount when evaluating children with suspected neurodegenerative disorders. A high index of suspicion is necessary when any combination of the following is present:

- Regression and progressive neurological deterioration
- Changes in personality or behavior
- Symptoms of refusal to feed, lethargy, vomiting, hypotonia, coma, or seizures in the neonatal or early infancy period.
- Focal neurological deficits, spasticity, and visual symptoms and signs
- Clumsiness or difficulties in gait
- Signs of jaundice, visceromegaly
- Dysmorphic features or coarse facies
- Parental consanguinity
- Positive family history of a similar illness/death

Adequate laboratory facilities to diagnose NDDD's are scarce and lacking in Uganda leading to delays in diagnosis, treatment and hence a poor prognosis in most cases. A multidisciplinary approach involving specialists from varied relevant disciplines is recommended in the management of neurodegenerative disorders. Management is geared towards the definitive treatment of the underlying disorder, the associated features and the complications with the provision of supportive therapy where required. Making the right and timely diagnosis is of critical importance for providing appropriate therapy, genetic counselling, guiding prognosis and implementation of preventive strategies. The ongoing studies of new techniques for imaging the central nervous system, discovery of the human genome and novel therapies for clinical treatment is expected to produce significant advances in the management of neurodegenerative disorders. It is hoped that our understanding of the genetics of these complex disorders will be improved, the changes in brain structure and function associated with them made more explicit and the prevention of the progression of the disorders in certain pre-symptomatic individuals curtailed.

References

1. Gore FM, Bloem PJ, Patton GC, Ferguson J, Joseph V, Coffey C, et al. Global burden of disease in young people aged 10–24 years: a systematic analysis. Lancet. 2011;377:2093–102.
2. Zhou Li, Miranda-Saksena M, Saksena NK. Viruses and neurodegeneration. Virol J. 2013; 10:172.
3. Forsyth RJ. Neurological and cognitive decline in adolescence. J Neurol Neurosurg Psychiatry. 2003;74:i9–16.
4. Wong V. Neurodegenerative diseases in children. Hong Kong Med J. 1997;3:89–95.

5. Jamison DT, Feachem RG, Makgoba MW, et al., editors. Disease and mortality in sub-Saharan Africa. 2nd ed. Washington, DC: World Bank; 2006.
6. Newton CR. Neurodevelopmental disorders in low- and middle-income countries. Dev Med Child Neurol (Commentary). 2012;54(12):1072.
7. Kakooza-Mwesige A, Ssebyala K, Karamagi C, Kiguli S, Smith K, Anderson MC, et al. Adaptation of the 'ten questions' to screen for autism and other neuro-developmental disorders in Uganda. Autism. 2014;18(4):447–57. 2013 Mar 27.
8. Maria BL. Current management in child neurology. 4th ed. Shelton: PMPH-USA; 2009.
9. Sridharan R, Radhakrishnan K, Ashok PP, Mousa ME. Prevalence and pattern of spinocerebellar degenerations in northeastern Libya. Brain. 1985;108(4):831–43.
10. Osuntokun BO, Adeuja AO, Schoenberg BS, Bademosi O, Nottidge VA, Olumide AO, et al. Neurological disorders in Nigerian Africans: a community-based study. Acta Neurol Scand. 1987;75(1):13–21.
11. Steele RG. Trajectory of certain death at an unknown time: children with neurodegenerative life-threatening illnesses. Can J Nurs Res. 2000;32(3):49–67.
12. Jan MM. Clinical approach to children with suspected neurodegenerative disorders. Neurosciences (Riyadh). 2002;7:2–6.
13. Forsyth RJ. Neurological and cognitive decline in adolescence. J Neurol Neurosurg Psychiatry. 2003;74:i9–16. doi:10.1136/jnnp.74.suppl_1.i9.
14. Johnson K. Trauma in the lives of children: crisis and stress management techniques for counsellors, teachers and other professionals. Alameda: Hunter House; 1998.
15. Dyken P, Krawiecki N. Neurodegenerative diseases of infancy and childhood. Ann Neurol. 1983;13:351–64.
16. Kaye EM. Update on genetic disorders affecting white matter. Pediatr Neurol. 2001;24: 11–24.
17. Swaiman K, Ashwal S, Ferriero D, editors. Pediatric neurology: principles and practice. 4th ed. Philadelphia: Elsevier; 2007.
18. Nobili F, Brugnolo A, Calvini P, et al. Resting SPECT-neuropsychology correlation in very mild Alzheimer's disease. Clin Neurophysiol. 2005;116:364–75.
19. UNAIDS/JC2502/1/E. Global report: UNAIDS report on the global AIDS epidemic 2013. Revised and reissued; November 2013. ISBN 978-92-9253-032-7.
20. UNAIDS. Report on the global AIDS epidemic. UNAIDS/WHO; 2012.
21. Little K, Thorne C, Luo C, Bunders M, Ngongo N, McDermott P, et al. Disease progression in children with vertically-acquired HIV infection in sub-Saharan Africa: reviewing the need for HIV treatment. Curr HIV Res. 2007;5(2):139–53.
22. Marum LH, Tindyebwa D, Gibb D. Care of children with HIV infection and AIDS in Africa. AIDS. 1997;11(B):S125–34.
23. Abubakar A, Van Baar A, Van de Vijver F, Holding P, Newton CJ. Paediatric HIV and neurodevelopment in sub-Saharan Africa: a systematic review. Trop Med Int Health. 2008;13(7):880–7.
24. Boyede GO, Lesi FEA, Ezeaka CV, Umeh CS. The neurocognitive assessment of HIV-infected school-aged Nigerian children. World J AIDS. 2013;3:124–30.
25. Bagenda D, Nassali A, Kalyesubula I, Sherman B, Drotar D, Boivin MJ, et al. Health, neurologic, and cognitive status of HIV-infected, long-surviving, and antiretroviral-naive Ugandan children. Pediatrics. 2006;117:729.
26. Bertou G, Thomaidis L, Spoulou V, Theodoridou M. Cognitive and behavioral abilities of children with HIV infection in Greece. Pediatrics. 2008;121(2):S100.
27. Valcour V, Sithinamsuwan P, Letendre S, Ances B. Pathogenesis of HIV in the central nervous system. Curr HIV/AIDS Rep. 2011;8:54–61.
28. Duiculescu D, Ene L, Radoi R, Ruta S, Achim CL. High prevalence and particular aspects of HIV-related neurological complications in a Romanian cohort of HIV-1 infected children and young adults. WEPDB 03 – IAS Sydney; 2007.
29. Ellis R, Heaton R, Letendre S, et al. Higher CD4 Nadir is associated with reduced rates of HIV-associated neurocognitive disorders in the CHARTER study: potential implications for early treatment initiation [Abstract 429]. 17th CROI 2010.

30. Letendre S, McClernon D, Ellis R, et al. Persistent HIV in the central nervous system during treatment is associated with worse ART penetration and cognitive impairment [Abstract 484b]. 16th CROI 2009.
31. Letendre S, FitzSimons C, Ellis R, et al. Correlates of CSF Viral loads in 1221 volunteers of the CHARTER cohort [Abstract 172]. 17th CROI 2010.
32. Simpson DM, Tagliati M. Neurologic manifestations of HIV infection. Ann Intern Med. 1994;121:769–85.
33. Cooper ER, Hanson C, Diaz C, et al. Encephalopathy and progression of human immunodeficiency virus in a cohort of children with perinatal acquired human immunodeficiency virus infection. Women and Infants Transmission Study Group. J Pediatr. 1998;132:808–12.
34. Mintz M. Neurological and developmental problems in pediatric HIV infection. J Nutr. 1996;126:2663s–73s.
35. Ojukwu IC, Epstein LG. Neurologic manifestations of infection with HIV. Pediatr Infect Dis J. 1998;17:343–4.
36. Xia C, Luo D, Yu X, Jiang S, Liu S. HIV-associated dementia in the era of highly active antiretroviral therapy (HAART). Microbes Infect. 2011;13:419–25.
37. Diesing TS, Swindells S, Gelbard H, Gendelman HE. HIV-1-associated dementia: a basic, science and clinical perspective. AIDS Read. 2002;12(8):358–68.
38. Working Group of the American Academy of Neurology AIDS Task Force. Nomenclature and research case definitions for neurologic manifestation of human immunodeficiency virus type 1 (HIV-1) infection. Neurology. 1991;41:778–85.
39. Chiriboga C, Fleishman S, Champion S, Gaye-Robinson L, Abrams E. Incidence and prevalence of HIV encephalopathy in children with HIV infection receiving highly active antiretroviral therapy (HAART). J Pediatr. 2005;146(3):402–7.
40. Bertou G, Thomaidis L, Spoulou V, Theodoridou M. Cognitive and behavioral abilities of children with HIV infection in Greece. Pediatrics. 2008;121(2):S100. doi:10.1542/peds.2007-2022BB.
41. Brewster DR, Kwiatkowski D, White NJ. Neurological sequelae of cerebral malaria in children. Lancet. 1990;336:1039–43.
42. Idro R, Marsh K, John CC, Newton CR. Cerebral malaria: mechanisms of brain injury and strategies for improved neurocognitive outcome. Pediatr Res. 2010;68(4):267–74.
43. Ibadin OM, Ofili NA, Momodu R, Oaikhena E, Oba I. Some economic and socio-cultural factors associated with cerebral malaria among under-fives in Benin city. Nigeria Niger J Paed. 2012;39(4):168–73.
44. Imani PD, Musoke P, Byarugaba J, Tumwine JK. Human immunodeficiency virus infection and cerebral malaria in children in Uganda: a case-control study. BMC Pediatr. 2011;11:5.
45. Rosario SM, Jesus TM, Benchimol C, Quinhentos V, Gonclaves L, et al. Transforming growth factor beta 2 and hemeoxygenase 1 genes are risk factors for the cerebral malaria syndrome in Angolan children. PLoS One. 2010;5(6):e11141.
46. Iloh GU, Chuku A, Amadi AN, Ofoedu JN. Proximate family biosocial variables associated with severe malaria disease among under-five children in resource-poor setting of a rural hospital in Eastern Nigeria. J Family Med Prim Care. 2013;2(3):256–62.
47. John CC, Bangirana P, Byarugaba J, Idro R, et al. Cerebral malaria in children is associated with long-term cognitive impairment. Pediatrics. 2008;122(1):e92–9.
48. Idro R, Kakooza-Mwesige A, Balyejjussa S, et al. Severe neurological sequelae and behaviour problems after cerebral malaria. BMC Res Notes. 2010;3:104.
49. Toro G, Roman G. Cerebral malaria: a disseminated vasculomyelinopathy. Arch Neurol. 1978;35:271.
50. Maneerat Y, Pongponratn E, Viriyavejakul P, Punpoowong B, Looareesuwan S, Udomsangpetch R. Cytokines associated with pathology in the brain tissue of fatal malaria. Southeast Asian J Trop Med Public Health. 1999;30(4):643–9.
51. Suri ML, Vijayan JP. Neurological sequelae of heat hyperpyrexia. JAPI. 1978;26:203–13.
52. Rubio JM, Buhigas I, Subirats M, Baquero M, Puente S, Benito A. Limited level of accuracy provided by available rapid diagnosis tests for malaria enhances the need for PCR-based reference laboratories. J Clin Microbiol. 2001;39(7):2736–7.

53. Farnert A, Arez AP, Babiker HA, et al. Genotyping of plasmodium falciparum infections by PCR: a comparative multicentre study. Trans R Soc Trop Med Hyg. 2001;95(2):225–32.
54. Newton CR, Peshu N, Kendall B, et al. Brain swelling and ischaemia in Kenyans with cerebral malaria. Arch Dis Child. 1994;70(4):281–7.
55. Nanyunja M, Lewis RF, Makumbi I, Seruyange R, et al. Impact of mass measles campaigns among children less than 5 years old in Uganda. J Infect Dis. 2003;187(1):S63–8. doi:10.1086/368026.
56. Canavan ME, Sipsma HL, Kassie GM, Bradley EH. Correlates of complete childhood vaccination in East African countries. PLoS One. 2014;9(4):e95709.
57. Biellik R, Madema S, Taole A, et al. First five years of experience with measles elimination in southern Africa: 1996–2000. Lancet. 2002;359:1564–8.
58. Inoue T, Kira R, Nakao F, et al. Contribution of the interleukin 4 gene to susceptibility to subacute sclerosing panencephalitis. Arch Neurol. 2002;59:822–7.
59. Yentur SP, Gurses C, Demirbilek V, et al. Alterations in cell-mediated immune response in subacute sclerosing panencephalitis. J Neuroimmunol. 2005;170:179–85.
60. Hara T, Yamashita S, Aiba H, et al. Measles virus-specific T helper 1/T helper 2-cytokine production in subacute sclerosing panencephalitis. J Neurovirol. 2000;6:121–6.
61. Gascon GG. Subacute sclerosing panencephalitis. Semin Pediatr Neurol. 1996;3:260–9.
62. Britt WJ. Slow viruses. In: Feigin R, Cherry J, editors. Textbook of pediatric infectious diseases. 4th ed. Philadelphia: W.B. Saunders Company; 1998. p. 646–65.
63. Centers for Disease Control. In: Atkinson W, Wolfe S, Hamborsky J, editors. Epidemiology and prevention of vaccine- preventable diseases. 12th ed. Washington, DC: Public Health Foundation; 2012.
64. Manayani DJ, Abraham M, Gnanamuthu C, Solomon T, Alexander M, Sridharan G. SSPE – the continuing challenge: a study based on serological evidence from a tertiary care centre in India. Indian J Med Microbiol. 2002;20:16–8.
65. Akram M, Naz F, Malik A, Hamid H. Clinical profile of subacute sclerosing panencephalitis. J Coll Physicians Surg Pak. 2008;18:485–8.
66. Campbell H, Andrews N, Brown KE, Miller E. Review of the effect of measles vaccination on the epidemiology of SSPE. Int J Epidemiol. 2007;36:1334–48.
67. Zilber N, Kahana E. Environmental risk factors for subacute sclerosing panencephalitis (SSPE). Acta Neurol Scand. 1998;98:49–54.
68. Koppel BS, Poon TP, Khandji A, Pavlakis SG, Pedley TA. Subacute sclerosing panencephalitis and acquired immunodeficiency syndrome: role of electroencephalography and magnetic resonance imaging. J Neuroimaging. 1996;6:122–5.
69. Prashanth LK, Taly AB, Ravi V, Sinha S, Rao S. Long term survival in subacute sclerosing panencephalitis: an enigma. Brain Dev. 2006;28:447–52.
70. Jabbour JT, Garcia JH, Lemmi H, Ragland J, Duenas DA, Sever JL. Subacute sclerosing panencephalitis. A multidisciplinary study of eight cases. JAMA. 1969;207:2248–54.
71. Hayashi M, Arai N, Satoh J, et al. Neurodegenerative mechanisms in subacute sclerosing panencephalitis. J Child Neurol. 2002;17:725–30.
72. Alkan A, Korkmaz L, Sigirci A, Kutlu R, et al. Subacute sclerosing panencephalitis: relationship between clinical stage and diffusion-weighted imaging findings. J Magn Reson Imaging. 2006;23(3):267–72.
73. Gutierrez J, Isaacson RS, Koppel BS. Subacute sclerosing panencephalitis: an update. Dev Med Child Neurol. 2010;52(10):901–7.
74. Sejvar JJ, Kakooza AM, Foltz JL, et al. Clinical, neurological, and electrophysiological features of nodding syndrome in Kitgum, Uganda: an observational case series. Lancet Neurol. 2013;12:166–74.
75. Korevaar DA, Visser BJ. Reviewing the evidence on nodding syndrome, a mysterious tropical disorder. Int J Infect Dis. 2013;17:e149–52.
76. Wasswa H. Ugandan authorities deal with a mysterious ailment that leaves people nodding continuously. BMJ. 2012;344:e349.

77. Aall L. Epilepsy in Tanganyika [review and newsletter]. Transcult Res Mental Hlth Probl. 1962;13:54–7.
78. Goudsmit J, van der Waals FW. Endemic epilepsy in an isolated region of Liberia. Lancet. 1983;1:528–9.
79. Lacey M. Nodding disease: mystery of southern Sudan. Lancet Neurol. 2003;2:714.
80. Centers of Disease Control. Nodding syndrome – South Sudan, 2011. MMWR Morb Mortal Wkly Rep. 2012;61:52–4.
81. Nyungura JL, Akim T, Lako A, et al. Investigation into the nodding syndrome in Witto Payam, Western Equatoria state, 2010. South Sudan Med J. 2011;4:3–6.
82. Uganda Ministry of Health. A report on the burden and epidemiology of nodding disease in the districts of Kitgum, Lamwo and Pader in Northern Uganda – August 2010. WHO; 1–2 Sept 2011.
83. Odongkara B, quoted by Wamboka L. Nodding disease calls for collective action: commentary in New Vision Newspaper. 2012;27(099):10.
84. Musisi S, Akena D, Nakimuli-Mpungu E, Okello J. Neuropsychiatric perspectives on nodding syndrome in northern Uganda: a case series study and a review of the literature. Afr Health Sci. 2013;13(2):205–18.
85. Idro R, Opoka RO, Aanyu HT, Kakooza-Mwesige A, Piloya-Were T, Namusoke H. Nodding syndrome in Ugandan children – clinical features, brain imaging and complications; a case series. BMJ Open. 2013;3:e002540.
86. Winkler AS, Friedrich K, Konig R, Meindl M, Helbok R, et al. The head nodding syndrome–clinical classification and possible causes. Epilepsia. 2008;49:2008–15.
87. Foltz J, Makumbi I, Sejvar J, Mugagga M, Ndyomugyenyi R, Atai-Omoruto AD, et al. Risk factors for nodding syndrome in Kitgum district, Uganda. PLoS One. 2013;8(6):e66419.
88. Centers for Disease Control and Prevention (CDC). Nodding syndrome-Sothern Sudan 2011. MMWR Morb Mortal Wkly Rep. 2012;61(3):52–4.
89. Coursin DB. Convulsive seizures in infants with pyridoxine-deficient diet. JAMA. 1954;154:406–8.
90. Grabow J, Linkswiler H. Electroencephalographic and nerve-conduction studies in experimental vitamin B6 deficiency in adults. Am J Clin Nutr. 1969;22:1429–34.
91. Van Der Kolk BA. Developmental trauma disorder. Towards a rational diagnosis for chronically traumatized children. Psychiatr Ann. 2005;35:401–8.
92. Dhossche DM, Kakooza-Mwesige A. Nodding syndrome in Ugandan children and adolescents: ménage à trois of epilepsy, (late-onset) autism, and pediatric catatonia. Autism-Open Access. 2012;2:3.
93. Dhossche DM, Ross CA, Stoppelbein L. The role of deprivation, abuse, and trauma in pediatric catatonia without a clear medical cause. Acta Psychiatr Scand. 2012;125:25–32.

Chapter 12
Cognitive Outcome of Malaria and HIV Infection in Children in Sub-Saharan Africa

Paul Bangirana

Abstract Infections of the Central Nervous System (CNS) are a public health burden for children in sub-Saharan Africa. In addition to their high mortality, they are a major cause of both major and subtle cognitive deficits in children. With the advent of more effective treatments, there is increased survival of these children meaning that more children who have suffered CNS infections are surviving into adulthood with consequent short or long term cognitive deficits. This chapter reviews the current literature on the cognitive deficits resulting from CNS malaria and HIV infection, the main causes of cognitive deficits in African children among the infectious diseases. It also looks at the factors associated with these cognitive deficits and reviews different interventions to prevent or improve outcome.

Keywords Central nervous system • Malaria • HIV/AIDS • Infection • Cognitive deficits • Rehabilitation

Introduction

Infections of the central nervous system are a public health burden for children in sub-Saharan Africa. In addition to their high mortality, they are a major cause of both major and subtle cognitive deficits in children. With the advent of more effective treatments, there is increased survival of these children meaning that more children are surviving into adulthood with short or long term cognitive deficits. This chapter reviews the current literature on the cognitive deficits resulting from malaria and HIV infection, the main causes of cognitive deficits in African children among the infectious diseases. It also looks at the factors associated with these cognitive deficits and reviews different interventions to prevent or improve outcome.

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S. Musisi, S. Jacobson (eds.), *Brain Degeneration and Dementia in Sub-Saharan Africa*, DOI 10.1007/978-1-4939-2456-1_12

Cognitive Outcomes of Malaria Infection in Children

During malaria infection, there is obstruction of blood through the capillaries due to sequestration of parasitized red blood cells, release of pro-inflammatory cytokines that affect the blood brain barrier integrity leading to metabolic derangement, seizures and coma [34]. Other less severe forms of malaria present with repeated seizures and impaired consciousness which can adversely affect the brain [16, 31]. In uncomplicated malaria and asymptomatic malaria, parasitemia present in the body may up-regulate hepcidin which in turn down-regulates iron absorption [19]. The resulting reduced iron intake and or unavailability is associated with a number of cognitive and behavioural problems [46]. The full spectrum of malaria illness from asymptomatic through symptomatic but non-severe malaria, to severe malaria (malaria with seizures and/or impaired consciousness, cerebral malaria) poses a potential risk to brain function leading to cognitive deficits. This review of the literature details the cognitive outcomes of the different forms of malaria and the risk factors.

Cognitive Outcome After Asymptomatic Malaria

Much emphasis has been placed on the severe forms of malaria due to their high mortality and resulting sequelae. Due to its role in malaria transmission, asymptomatic malaria, until recently has not been considered of much clinical concern, but it is now gaining important consideration [27]. High rates of asymptomatic malaria have been observed in African children with rates as high as 80 % in the wet seasons [27, 43]. Two studies have so far evaluated the effects of asymptomatic malaria on cognition in children.

In a study to assess the effect of asymptomatic malaria on cognition, Al Serouri et al. [1] compared 445 Yemeni children with asymptomatic malaria to 142 children matched for grade and school on tests of verbal fluency, working memory, sustained attention, psychomotor speed, fine motor coordination and visual recognition [1]. Two weeks later, 150 children still asymptomatic were compared to 150 children whose parasitemia cleared on the above tests. Regression analysis controlling for age, socioeconomic status and nutrition found fine motor coordination to be the only cognitive ability affected by asymptomatic malaria. Parasite density predicted fine motor coordination scores at baseline and improvement in visual recall after parasite clearance. No significant change in cognitive scores was noticed 2 weeks later between those who were still asymptomatic and those whose parasites cleared. Other factors associated with cognitive test performance were anemia, wealth factor and age. The authors concluded that parasitemia may affect fine motor skills and visual recall.

In a Ugandan study, Nankabirwa et al. [50] carried out a study to assess the association between anemia, asymptomatic malaria and cognition in Ugandan

school children aged 6–14 years [50]. They assessed sustained attention and abstract reasoning in 740 children as well as, sociodemographic variables, helminth infection and haemoglobin. About 30 % of the children had asymptomatic malaria. Multiple regression analyses controlling for sex, age, weight for age Z score, helminth infection, anemia, socioeconomic status and maternal education showed an association between asymptomatic malaria and sustained attention (adjusted mean difference: −1.6, 95 % CI: −2.49 to −0.81) and abstract reasoning (−0.6, 95 % CI: −1.01 to −0.21). Higher parasitemia was associated with lower attention scores. Unlike the study by Al Serouri et al. [1], anemia was not associated with any cognitive outcome in this study. They concluded that effect of asymptomatic malaria on cognition could be a result of repeated infections or an immunological pathway.

These studies suggest that asymptomatic malaria affects cognition in children though it is not clear how this occurs since both studies reported slightly differing results. In the Yemeni study, being anemic (haemoglobin ≤90 g/l) was associated with lower cognitive scores which was not the case in the Ugandan study. Nankabirwa et al. [50] showed that higher parasitemia affected sustained attention scores while Al Serouri et al. [1] reported that asymptomatic children who became parasite free 2 weeks later did not show an improvement in cognitive scores, implying that parasite presence is mostly likely not the main cause for low cognitive scores.

Cognitive Outcome After Non-severe Malaria

Fernando and colleagues have carried out a series of studies looking at the effect of uncomplicated malaria on cognitive outcome and school performance in children. They followed up 571 children aged 1–8 years for 6 years from 1992 and recorded the number of malaria episodes [26]. Children's scores in mathematics and language in 1997 were associated with the number of malaria episodes. Those who experienced three or less episodes scored 15 % higher than those with more episodes. These findings were replicated in a cross sectional study where they assessed the effect of repeated malaria attacks on measures of writing, reading skills, letter reading, sentence structure and mathematics in 325 children aged 4–6 years [25]. Children were tested at one time point and number of malaria episodes suffered in their life time recorded. Total number of malaria attacks was associated with letter reading and languages scores, where those not experiencing any malaria episode had scores 19 % higher than those who had five or more episodes for letter reading and 4.3 % for language. They later investigated the short term impact of an acute malaria episode on tests of mathematics and language where 199 children with malaria and 144 children with non malaria fever were tested at presentation to a health facility and 2 weeks later after treatment of the malaria bout [24]. A control group of 305 healthy children were also given the same tests. Children with malaria performed significantly poorer in mathematics and language at both time points compared to the controls. Those with non malaria fever also had poorer scores at

baseline but not at follow-up. Contrary to expected results, higher haemoglobin was associated with poorer scores in mathematics and language.

Recently Thuilliez and colleagues followed up 227 Malian children for 8 months recording malaria episodes, socioeconomic variables and cognition [55]. Children who had not experienced any malaria episode had better scores than those who had malaria in the follow-up period. In addition, higher parasitemia was associated with lower cognitive scores. The effect of anemia on cognition was however not conclusive. Malaria was also the most common cause of absenteeism from school.

Contrary to all the above findings, Halliday and colleagues did not observe any effect by either malaria infection or anemia during malarial illness on sustained attention, literacy, cognition or numeracy in 2,400 Kenyan children [29]. Other non-health related variables like age, gender, socioeconomic status, parental education and school environment were associated with cognitive outcomes suggesting health status (single malaria episode or anemia) may not be predictive of cognition in children in moderate malaria transmission areas after non-severe malaria.

Despite these findings from Halliday et al. [29], the preceding studies provide strong evidence that uncomplicated malaria affects cognition and academic performance in children with number of malaria episodes being the best predictor of outcome. The mechanisms for the effect on cognition are not clearly understood.

Cognitive Outcome After Complicated Malaria

Effect of Malaria with Impaired Consciousness on Cognition

Holding et al. assessed cognitive outcomes in 87 children who had malaria with impaired consciousness 42–70 months after the illness [31]. An equal number of age matched controls also completed the same battery of tests. More children in the malaria group were cognitively impaired (14 %) compared to 4 % in the control group with hypoglycaemia and coma score less than 2 independently associated with cognitive impairment. All children who had a coma score less than 2 were cognitively impaired. This group with a coma score less than 2 meets the criteria for cerebral malaria (CM) which makes it difficult to make conclusions about the effect of malaria with impaired consciousness on cognition. This is because some of those found to be impaired may have had a clear diagnosis of CM.

Effect of Malaria with Repeated Seizures on Cognition

Convulsions are a common feature in childhood malaria in African children and are predictive of neurological outcome and mortality [33, 32]. Carter et al. studied cognitive outcomes in 156 Kenyan children aged 6–9 years with a history of malaria with multiple seizures (MS) [16]. The median time from admission to

assessment was 71 months (IQR 55–85 months). An age matched group of 179 children without a history of MS were also enrolled as a control group. Children were given tests for speech and language, attention, motor skills, non-verbal skills, memory, hearing and vision and behaviour. Although the two groups did not differ much on most tests, 23.7 % of those with malaria had impairment in at least one of the above areas compared to 10.1 % in the controls. No effect was observed on memory in this study and in a later analysis of everyday memory in this same group [41].

In a subsequent study to assess speech and language functions after malaria with multiple seizures, Carter and colleagues administered tests for receptive grammar, receptive vocabulary, syntax, lexical semantics, higher level language, pragmatics and phonology and word finding [17]. The MS group had 9 % impaired in at least one of the areas tested compared to 2 % of the controls. The malaria group were three times more likely to develop speech and language impairment than the controls (OR = 3.12, 95 % CI = 0.9–10.8, p = 0.07).

These studies are evidence that MS is associated with cognitive, motor, behavioural and speech and language deficits in children. The above studies were carried out over 7 years after the illness in some of the children indicating the longterm effects of malaria with multiple seizures. The risk factors for these deficits were not identified although children with active epilepsy performed worse than those without epilepsy [16]. Active epilepsy is a likely consequence of severe malaria as surviving children tend to progressively have more seizures at 24 months [53].

Effect of Severe Malarial Anemia on Cognition in Children

Severe malarial anemia (SMA) is the commonest form of severe malaria affecting up to five million children annually [49]. Asymptomatic and uncomplicated malaria are associated with poor cognitive outcome in children as noted above. In addition, anemia is also associated with poor cognitive outcome [52]. This implies that SMA affecting several children in Africa could also be a major cause of cognitive deficits in children. In a recent study among Ugandan children aged 18 months to 4.9 years, neurocognitive test scores of a group that survived SMA was compared to community controls [6]. Attention, memory and overall cognition were assessed a week after discharge, and at 6 and 12 months. The SMA group had poorer scores in cognitive ability than the community controls. Attention scores were also lower but not significantly. The difference in age adjusted Z scores for overall cognition between the SMA group and community controls was half a standard deviation (−0.52) analogous to 8 IQ points. To our knowledge, this is the first study demonstrating the effects of SMA on cognition. It provides further evidence of malaria's effect on children's cognition as shown by the difference of about 8 IQ points 12 months after the illness.

Effect of Cerebral Malaria on Cognition in Children

The effects of CM on cognition have been studied more than any other malaria form. Cerebral Malaria (CM) is caused by P. Falciparum and is associated with alterations in consciousness, coma, convulsions and high fever. Retrospective studies show that neurocognitive deficits are common in children with a history of CM with coma duration, deep coma, multiple seizures on admission, duration of seizures, malnutrition and hypoglycaemia associated with these deficits [9, 22, 33, 40, 42]. Prospective studies have gone further to describe the progression of these sequelae in children. John and colleagues assessed memory, learning and attention at baseline, 3, 6 and 24 months in 44 children with CM compared to 54 with uncomplicated malaria [11, 36]. Scores were compared to 89 community controls. At 3 months, 19 % of the CM group were impaired in at least one of the three areas tested compared to 7 % of the controls ($p=0.07$). The impairment rate in the CM group increased at 6 months (21.5 % vs. 5.7 %, $p=0.01$) and at 24 months (26.3 % vs. 7.6 %, $p=0.006$) with attention being the most affected. Children with CM had a 3.67 fold increased risk of developing cognitive impairment compared to the controls [36].

This first prospective study of the cognitive sequelae of CM demonstrated that children with a history of CM have a slower developmental trajectory than their peers who had no CM. It also collaborates with earlier retrospective studies which showed long-term deficits after CM [16]. Factors associated with cognitive deficits at 6 months were coma duration and number of seizures while diminished tendon reflexes and neurological deficits at 3 months were associated with cognitive impairment at 24 months. Elevated CSF tumour necrosis factor alpha was correlated with attention and memory scores at 6 months [37].

Malaria retinopathy is now as a distinctive feature of CM that helps improve the diagnosis of the disease [7]. This is because children diagnosed with CM without malaria retinopathy have other pre-existing developmental delays and a family history of epilepsy [7] which may contribute to the cognitive deficits thus over estimating the cognitive burden of CM. Birbeck and colleagues carried out a prospective study to determine whether retinopathy confirmed CM is a risk factor for epilepsy and new neuro-disabilities [8]. They recruited 132 children with retinopathy confirmed CM and 264 controls (non comatose sick children) and followed them up for 544 days. The CM group were at increased risk for epilepsy (OR undefined, $p<0.00001$) and new neurodisabilities (OR 37.8, 95 % CI 8.8–161.8; $p<0.0001$). Further study of a sample of these children showed the CM group to have neurodevelopmental delay (OR 2.13, 95 % CI 1.09–4.19; $p<0.028$) especially in language [14]. Seizures during admission and high temperature were associated with epilepsy while platelet count, lactate and coma duration were associated with neurodevelopmental delay [8, 14].

A recent prospective study in Ugandan children below 5 years old assessed general cognition, memory and attention in children with CM a week after discharge and at 6 and 12 months later [6]. Test scores were compared to a group with SMA and a community control group. Children with CM had poorer scores in all domains

than the community control group at 12 months. The difference in age adjusted Z scores at 12 months between the CM group and the community controls was almost a full standard deviation (−0.85) analogous to 13 IQ points. Longer coma duration, deeper coma, number of seizures and neurologic deficits at 6 and 12 months were associated with lower cognitive outcomes. Presence of retinopathy did not affect the outcome as CM survivors with and without retinopathy did not differ in test performance and retinopathy did not modify the effect of CM on cognition.

These studies provide strong evidence that CM is associated with cognitive deficits in children which persist for some years after the illness. These deficits are also associated with clinical and laboratory factors involved in the disease pathogenesis implying adjuvant treatments targeting these factors may improve cognitive outcome.

Interventions to Prevent Cognitive Deficits or Improve Outcome After Malaria Infection

Primary Prevention

Primary prevention interventions will target prevention of malaria infection in order to remove the risk of these cognitive deficits. Malaria prevention approaches include; vaccination, vector control (insecticide-treated bed net use, indoor residual spraying), chemoprevention and chemoprophylaxis [58]. Chemoprevention reduces the incidence of malaria, parasitemia and anemia both of which are independently associated with poor cognitive outcome [51]. In Gambia, Jukes et al. assigned 1,190 children under 5 years of age to either chemoprophylaxis or placebo for 4 years during the malaria transmission season and followed up 14 years later [39]. No significant differences were seen in mental development scores between the treatment groups. Children who received chemoprevention achieved just over half a grade higher in school, a significant difference compared to controls. Clarke et al. assigned 6,758 children aged 5–18 years to intermittent preventive treatment (IPT) or a placebo [18]. At 12 months post intervention, the IPT group had a lower prevalence of anaemia and had higher attention scores than the placebo group. No trials have evaluated the effect of the other malaria prevention interventions on cognition.

Secondary Prevention

Secondary prevention of cognitive outcomes in children infected with malaria involves administration of effective treatments and or using adjunct therapies to combat disease processes associated with cognitive impairment. In severe malaria, artesunate is more effective than quinine in reducing mortality and also reducing

seizures and coma depth, two clinical features associated with poor cognitive outcome [20]. There was no significant difference in neurological outcome at 28 days between the groups. However trials for adjunct therapies for severe malaria have not been successful in reducing mortality, coma or seizures [38].

Tertiary Prevention

Children surviving severe malaria are at risk for cognitive impairment with 1 in 4 going on to have long term cognitive impairment [36]. Trials using computerised cognitive rehabilitation training in African children surviving CM have shown benefits in cognition and behaviour suggesting that interventions carried out after the disease may be beneficial [3, 5]. In these trials, children were assigned to 16 sessions, each last 45 min delivered over 8 weeks (two sessions per week). Children completed cognitive exercises training memory, attention, visuomotor and reasoning. These studies however did not have an active control group that was also exposed to computers, had no long term follow-up and it is not known which of the four categories of cognitive exercises are more effective or whether benefit can be obtained by training one skill as has been done successfully for ADHD [44]. Despite these limitations, they do improve cognition in children surviving severe malaria.

Effect of HIV on Cognition in Children

The HIV virus is transported into the brain through the blood brain barrier by infected monocytes which in turn differentiate into macrophages that reproduce the virus in the brain. Infected CD4 T lymphocytes may also transport the virus into the brain [28]. As a result of HIV entry in the brain, activated microglia and macrophage release quinolinic acid, tumor necrosis factor, platelet activating factor, and arachidonic acid metabolites which impair blood brain barrier function resulting in widespread inflammation in the brain [28, 23].

Cognitive Outcomes of HIV Infection in Antiretroviral Therapy (ART) Naive Children

The earliest studies on the effect of HIV on African children's cognition were carried out in the pre-ART era. Msellati and colleagues in Rwanda compared neurodevelopmental outcome (gross motor, fine motor, social contact and language) of perinatally HIV infected children to two control groups; HIV negative children born to HIV positive mothers (HIV exposed) and HIV negative children born to uninfected

mothers (HIV unexposed) [48]. Tests were done at 6, 12, 18 and 24 months of age. The HIV positive children had a higher frequency of abnormal neurodevelopmental assessments than the control groups at 6 months (16 vs. 3.3, p=0.0001), 12 (31 vs. 7.7, p=0.0001), 18 (40 vs. 7.9, p=0.0001) and 24 (15 vs. 2.2, p=00001). Gross motor was the most affected area which had significantly poorer scores at all the three time points. The HIV exposed and unexposed groups did not differ in any of the neurodevelopmental areas tested. No risk factors for abnormal neurodevelopmental assessment were identified though the frequency of an abnormal assessment was much higher in children with clinical AIDS (ranging from 22 % to 87.5 % at the four time points).

A study by Boivin et al. in Zaire (now Democratic Republic of Congo) assessed two groups of children for cognition [10]. In the first sub-study among children below 2 years, 14 perinatally infected children were compared to 20 exposed and 16 unexposed children on tests of gross motor, fine motor, language and personal-social skills. Testing was done at 3, 6, 9, 12 and 18 months of age. Repeated measures analysis of variance showed the HIV group had poorer gross motor, fine motor and personal-social skills than the other groups. Similar to the previous study by Msellati and colleagues [48], there were no differences in outcome between the exposed and unexposed groups. In the second sub-study with children over 2 years of age, 11 children perinatally infected were compared to 15 exposed and 15 unexposed children on tests of cognition, language, motor, sequential processing, simultaneous processing, nonverbal reasoning and mental processing composite. The HIV infected group had poorer scores in motor, sequential processing, simultaneous processing, nonverbal reasoning and mental processing composite. Contrary to the earlier studies above, the exposed group performed poorer on many of the neurodevelopmental outcomes compared to the unexposed group.

Drotar and colleagues [21] carried out a larger study in Ugandan children using the same groupings from the above two studies (infected, exposed and unexposed) [21]. Seventy nine HIV infected children were followed up from birth and compared to 241 exposed and 116 unexposed children on tests of mental development, motor and information processing. Testing for mental development and motor was done at 6, 9, 12, 18 and 24 months while information processing was assessed at 6, 9 and 12 months. A test score was categorised as impaired if it was more than two standard deviations below the mean of the unexposed group. The HIV infected group had more children with impaired motor scores at all the five time points and more children with impaired mental development at 6 and 18 months only. There were no differences in information processing scores between the three groups. No risk factors for motor and mental development deficits were identified.

In a follow study of the Drotar et al. [21] cohort 6 years later, Bagenda et al. assessed cognition (Sequential Processing and Simultaneous Processing) and academic achievement (Reading, Spelling and Arithmetic) in 28 HIV infected, 42 exposed and 37 unexposed children [2]. The HIV exposed group had higher scores than the HIV infected group in the Sequential Processing measure of Hand Movements (8.1 vs. 10.4, p=0.02) and in the academic achievement measure of Reading (62.1 vs. 73.2, p=0.009). There were no other differences in simultaneous and sequential processing subscales and in reading, writing and arithmetic between

the groups. The authors concluded that the high mortality in the HIV infected group may have selected children who had more CNS involvement leaving behind children that have average cognition functioning. However other factors that differed between the groups were not controlled like the anthropometric results. Secondly, being a school going age, education exposure was not factored in the analyses. These factors are associated with cognitive functioning in Ugandan children of the same age range [4].

Ruel and colleagues [54] conducted a study that addressed some of the limitations in the above studies when they assessed cognition in HIV infected Ugandan children who had high CD4 counts thus ineligible for ART [54]. They examined the effect of HIV, including clinical stage, on cognition and controlled for other socioeconomic variables that may affect cognition like age, sex, socioeconomic status and quality of the home environment. HIV infected children had poorer reaction time, general cognition, working memory, visuospatial processing, reasoning and motor scores than a control group of HIV negative children. When children in clinical stages 1 and 2 were compared to controls, only visuospatial processing, reasoning and motor skills were impaired implying most deficits were in those in stage 3. Another study found that in this group of HIV infected children, those having subtype A had poorer performance in working memory and visuospatial skills than those with subtype D [13]. The conclusion from this study is that HIV infected children who are asymptomatic are already CNS comprised with several cognitive deficits that may affect other functional areas, with subtype A more at risk of these deficits. ART initiation may therefore be needed earlier and may need to consider drugs with greater CNS penetration for those with subtype A. The effect of time of infection (peri- or post-natal) was not assessed in this study.

In an attempt to study the association between time of infection and neurodevelopmental outcome, McGrath et al. assessed mental development and psychomotor development in HIV infected Tanzanian children at 6, 12 and 18 months of age and compared them to HIV negative children [47]. Children infected with HIV were categorised as infected within the first 21 days or after 21 days. Children infected within the first 21 days had lower mental and motor performance than the controls at all time points while those infected after 21 days also had poorer performance but not significantly for mental performance at 6 and 18 months. Motor performance had higher mean differences than mental performance for all time points in both HIV groups. Testing HIV positive at birth was associated with a 14.9 times higher risk of being delayed in mental development while testing positive after birth was associated with a 3.2 times higher risk than the HIV negative children. Children already infected at birth are thus more likely to have poorer neurodevelopmental outcome than those infected later. The authors concluded that early infection could interfere with the myelination process affecting projection fibres and association and commissural connections resulting in global deficits including motor abnormalities. Later interference with myelination could affect commissural connections and connection with the poles of the cerebral lobes affecting cognitive functions.

Further insight into the pathogenesis of these cognitive deficits in asymptomatic HIV infected children is from imaging studies. Hoare et al. assessed neuropsychological performance and diffusion tensor images in 12 highly active antiretroviral therapy (HAART) naive HIV infected children. Similar assessments were done in 12 controls matched for age, gender and race. HIV infected children had poorer neuropsychological test performance in general intelligence, motor functioning, processing speed, visuospatial processing, memory and executive function. In the HIV groups, there was decreased fractional anisotropy and increased radial diffusivity in the corpus callosum, increased radial diffusivity and mean diffusivity in the superior longitudinal fasciculus. These imagining findings are indicative of white matter damage and myelin loss in the corpus callosum and superior longitudinal fasciculus [30]. Poor test performance correlated with imaging abnormalities in the corpus callosum and superior longitudinal fasciculus. This study shows that damage to the white matter and demyelination are important factors in the pathogenesis of cognitive deficits in HIV infected children.

Cognitive Outcomes of HIV Infection in HAART Exposed Children

There are clear benefits of HAART treatment on cognitive functioning in African children. Van Rie et al. [56] assessed cognition in 35 HIV infected Congolese children and compared them to 35 exposed and 90 unexposed children [56]. The HIV infected group had more mental and motor developmental delays than the unexposed group (60 % vs 24 %, $p<0.0001$ and 29 % vs 0 %, $p<0.0001$ respectively). The exposed group also had more children with mental and developmental delays than the unexposed group (40 % vs 24 %, $p<0.09$ and 14.3 % vs 0 %, $p<0.0005$ respectively). Compared to the unexposed group, there were more language comprehension and language expression delays in the HIV infected (77 % vs 13 %, $p<0.0001$ and 85 % vs 13 %, $p<0.0001$ respectively) and exposed groups (11 % vs 13 %, $p<0.99$ and 47 % vs 13 %, $p<0.018$ respectively). Contrary to previous studies using the same measures (Bayley Scales of Infant Development), children in this study had motor development less affected than mental development.

When these children were initiated into HIV care (including HAART) and given cognitive testing at 6 and 12 months later, improvement in mental and motor development were observed [57]. Children who presented early for care (at clinical stage 1 or 2) had better motor scores at all time points than those who presented late. Young children ($\leq$29 months) and not older children (>29 months) had an accelerated gain in motor and cognitive scores over the 12 months. This study suggests that HIV care and treatment may improve cognitive development in children especially once initiated early. This study shows the importance of early initiation of HAART given the results in McGrath et al. [30] where children who were infected earlier had poorer cognitive outcomes than those detected much later [47].

Laughton and colleagues assessed the benefits of early versus deferred HAART on cognitive outcome in children [45]. Children were randomly assigned to early HAART (n = 64, given within 3 months) or deferred HAART (n = 26, given when there was clinical or immunological progression to AIDS) and assessed for locomotor, personal-social skills, hearing & language, eye & hand coordination, and performance (fine motor and visuospatial skills) using the Griffiths Mental Development Scales. Two control groups of HIV exposed and unexposed children were also assessed. Children in the early treatment group had better Locomotor scores than the deferred group. The early treatment group also had similar scores to the uninfected control groups for all scores except locomotor where the exposed arm had better scores. The effect of early HAART on cognition compared to the deferred group as well as the comparative performance of the early HAART group to the control groups highlights the importance of early therapy on CNS integrity in HIV infected children.

Interventions to Prevent Cognitive Deficits due to HIV Infection

Primary Prevention

Prevention (or elimination) of mother to child transmission of HIV is one intervention preventing the spread of HIV to children born to HIV infected mothers. However no trials have been conducted to assess cognitive outcomes in children whose mothers received PMTCT and those who did not. Studies comparing cognitive outcome in HIV infected children and HIV negative exposed children (born to HIV infected mothers) do provide evidence that PMTCT could prevent cognitive deficits resulting from HIV infection in young children. Van Rie et al. [56] observed more mental and motor development delays in HIV infected children compared to the exposed children [56]. However earlier studies did not see any differences between the exposed and the HIV infected groups [10, 48]. In one sub-study by Boivin et al. the exposed group had poorer cognitive outcomes than the HIV negative unexposed children [10]. This latter finding suggests that environmental variables like caregiver characteristics may also play a role in determining cognitive functioning in children necessitating interventions targeting them.

Secondary Prevention

For children infected with HIV, early initiation of treatment may delay the progression to severe disease leading to better cognitive outcomes. Studies by Van Rie et al. [57] and Laughton et al. [45] show that children who present to care in the early stages of the disease and those who receive HAART within 3 months have better cognitive outcomes than those who present for treatment later or receive treatment

after 3 months [57, 45]. However HAART alone may not improve cognitive outcome as Jeremy et al. [35] noted necessitating additional interventions [35].

Tertiary Prevention

Like for children surviving severe malaria, computerised cognitive rehabilitation training (CCRT) has also improved cognitive outcome in children infected with HIV. Boivin and colleagues randomized children to either cognitive training or a non intervention arm [12]. Ten sessions of 45 min each were completed in 5 weeks for the intervention arm training memory, attention, visuomotor and reasoning. The intervention group had better outcomes on learning and attention compared to the control group. In recognition of the effect of the care giving environment on cognitive outcome, Boivin and colleagues piloted an intervention aimed at improving the child-caregiver relationship and assessed the cognitive benefits in HIV infected children [15]. The intervention involved a 12 month structured caregiver training that emphasised nurturing children through interacting with the environment in ways that enhance their cognitive development. Children were randomised to either the caregiver training intervention or to a health and nutrition training. Children in the intervention had better visual reception and memory, their mothers were less depressed and they had better interaction with their mothers at the end of the intervention compared to the control group. This caregiver intervention shows promise in improving cognition in children with HIV since it is implemented in the community and does not require specialised equipment like CCRT. A trial is underway in Uganda to look at the long term benefits of this intervention and whether the caregiver training improves cognition in other children in the household.

Conclusion

Malaria infection, from asymptomatic to severe disease is associated with cognitive deficits whose severity increases along the disease spectrum. Clinical features of the disease are associated with cognitive outcome and these should be the focus of adjunct therapies to prevent poor cognition. Unfortunately, trials for adjunct therapies have not been successful while the long benefit of cognitive training interventions in severe malaria survivors is not known. Chemoprevention trials are the best solution at present as they reduce disease burden and also result in better cognitive outcomes in children.

HIV infection is associated with cognitive deficits in African children with motor difficulties being commonly reported. These deficits are associated with white matter loss, demyelination and having subtype A. The effects on cognition may also be an indirect effect through deficient caregiving from the infected mother as seen in poorer test scores in the exposed but negative children. Early initiation of treatment, cognitive training and improving the caregiver-children interaction may improve cognitive outcome.

References

1. Al Serouri AW, Grantham-McGregor SM, Greenwood B, Costello A. Impact of asymptomatic malaria parasitaemia on cognitive function and school achievement of schoolchildren in the Yemen Republic. Parasitology. 2000;121(4):337–45.
2. Bagenda D, Nassali A, Kalyesubula I, Sherman B, Drotar D, Boivin MJ, Olness K. Health, neurologic, and cognitive status of HIV-infected, long-surviving, and antiretroviral-naive Ugandan children. Pediatrics. 2006;117(3):729–40.
3. Bangirana P, Giordani B, John CC, Page C, Opoka RO, Boivin MJ. Immediate neuropsychological and behavioral benefits of computerized cognitive rehabilitation in Ugandan pediatric cerebral malaria survivors. J Dev Behav Pediatr. 2009;30(4):310–8.
4. Bangirana P, John CC, Idro R, Opoka RO, Byarugaba J, Jurek AM, Boivin MJ. Socioeconomic predictors of cognition in Ugandan children: implications for community interventions. PLoS One. 2009;4(11):e7898.
5. Bangirana P, Allebeck P, Boivin MJ, John CC, Page C, Ehnvall A, Musisi S. Cognition, behaviour and academic skills after cognitive rehabilitation in Ugandan children surviving severe malaria: a randomised trial. BMC Neurol. 2011;11(1):96.
6. Bangirana P, Opoka RO, Boivin MJ, Idro R, Hodges JS, Romero RA, Shapiro E, John CC. Severe malarial anemia is associated with long-term neurocognitive impairment. Clin Infect Dis. 2014. doi:10.1093/cid/ciu293. Oxford University Press.
7. Birbeck GL, Beare N, Lewallen S, Glover SJ, Molyneux ME, Kaplan PW, Taylor TE. Identification of malaria retinopathy improves the specificity of the clinical diagnosis of cerebral malaria: findings from a prospective cohort study. Am J Trop Med Hyg. 2010;82(2):231–4.
8. Birbeck GL, Molyneux ME, Kaplan PW, Seydel KB, Chimalizeni YF, Kawaza K, Taylor TE. Blantyre Malaria Project Epilepsy Study (BMPES) of neurological outcomes in retinopathy-positive paediatric cerebral malaria survivors: a prospective cohort study. Lancet Neurol. 2010;9(12):1173–81.
9. Boivin MJ. Effects of early cerebral malaria on cognitive ability in Senegalese children. J Dev Behav Pediatr. 2002;23(5):353–64.
10. Boivin MJ, Green SD, Davies AG, Giordani B, Mokili JK, Cutting WA. A preliminary evaluation of the cognitive and motor effects of pediatric HIV infection in Zairian children. Health Psychol. 1995;14(1):13–21.
11. Boivin MJ, Bangirana P, Byarugaba J, Opoka RO, Idro R, Jurek AM, John CC. Cognitive impairment after cerebral malaria in children: a prospective study. Pediatrics. 2007;119(2):e360–6.
12. Boivin MJ, Busman RA, Parikh SM, Bangirana P, Page CF, Opoka RO, Giordani B. A pilot study of the neuropsychological benefits of computerized cognitive rehabilitation in Ugandan children with HIV. Neuropsychology. 2010;24(5):667–73. US: American Psychological Association.
13. Boivin MJ, Ruel TD, Boal HE, Bangirana P, Cao H, Eller LA, Charlebois E, et al. HIV-subtype A is associated with poorer neuropsychological performance compared with subtype D in antiretroviral therapy-naive Ugandan children. AIDS. 2010;24(8):1163–70.
14. Boivin MJ, Gladstone MJ, Vokhiwa M, Birbeck GL, Magen JG, Page C, Semrud Clikeman M, Kauye F, Taylor TE. Developmental outcomes in Malawian children with retinopathy positive cerebral malaria. Trop Med Int Health. 2011;16(3):263–71. Wiley Online Library.
15. Boivin MJ, Bangirana P, Nakasujja N, Page CF, Shohet C, Givon D, Bass JK, Opoka RO, Klein PS. A year-long caregiver training program improves cognition in preschool Ugandan children with human immunodeficiency virus. J Pediatr. 2013;163(5):1409–16. Elsevier.
16. Carter JA, Ross AJ, Neville BG, Obiero E, Katana K, Mung'ala-Odera V, Lees JA, Newton CR. Developmental impairments following severe falciparum malaria in children. Trop Med Int Health. 2005;10(1):3–10. doi:10.1111/j.1365-3156.2004.01345.x. TMI1345 [pii].

17. Carter JA, Lees JA, Gona JK, Murira G, Rimba K, Neville B G, Newton C R. Severe falciparum malaria and acquired childhood language disorder. Dev Med Child Neurol. 2006;48(1):51–57. S0012162206000107 [pii] doi:10.1017/S0012162206000107. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16359594
18. Clarke SE, Jukes MC, Njagi JK, Khasakhala L, Cundill B, Otido J, Crudder C, Estambale BB, Brooker S. Effect of intermittent preventive treatment of malaria on health and education in schoolchildren: a cluster-randomised, double-blind, placebo-controlled trial. Lancet. 2008;372(9633):127–38. S0140-6736(08)61034-X [pii] doi:10.1016/S0140-6736(08)61034-X. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18620950
19. De Mast Q, Van Dongen-Lases EC, Swinkels DW, Nieman A-E, Roestenberg M, Druilhe P, Arens TA. Mild increases in serum hepcidin and interleukin-6 concentrations impair iron incorporation in haemoglobin during an experimental human malaria infection. Br J Haematol. 2009;145(5):657–64. doi:10.1111/j.1365-2141.2009.07664.x. Blackwell Publishing Ltd.
20. Dondorp AM, Fanello CI, Hendriksen ICE, Gomes E, Seni A, Chhaganlal KD, Bojang K, Olaosebikan R, Anunobi N, Maitland K. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. Lancet. 2010;376(9753):1647–57. Elsevier.
21. Drotar D, Olness K, Wiznitzer M, Guay L, Marum L, Svilar G, Hom D, Fagan JF, Ndugwa C, Kiziri-Mayengo R. Neurodevelopmental outcomes of Ugandan infants with human immunodeficiency virus type 1 infection. Pediatrics. 1997. 100(1):E5. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9200379
22. Dugbartey AT, Spellacy FJ, Dugbartey MT. Somatosensory discrimination deficits following pediatric cerebral malaria. Am J Trop Med Hyg. 1998. 59(3):393–96. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9749631
23. Eggert D, Anderson E, Zheng JL, Gendelman HE, Goodkin K, Shapshak P, Verma A. Chemokines and the neuropathogenesis of HIV-1 infection. The spectrum of neuro-AIDS disorders: pathophysiology, diagnosis, and treatment. 2009:151–71. ASM Press, Washington DC.
24. Fernando D, de Silva D, Wickremasinghe R. Short-term impact of an acute attack of malaria on the cognitive performance of schoolchildren living in a malaria-endemic area of Sri Lanka. Trans R Soc Trop Med Hyg. 2003;97(6):633–9. S0035-9203(03)80093-7 [pii].
25. Fernando D, Wickremasinghe R, Mendis KN, Wickremasinghe AR. Cognitive performance at school entry of children living in malaria-endemic areas of Sri Lanka. Trans R Soc Trop Med Hyg. 2003;97(2):161–5.
26. Fernando SD, Gunawardena DM, Bandara MR, De Silva D, Carter R, Mendis KN, Wickremasinghe AR. The impact of repeated malaria attacks on the school performance of children. Am J Trop Med Hyg. 2003;69(6):582–8.
27. Geiger C, Agustar HK, Compaore G, Coulibaly B, Sie A, Becher H, Lanzer M, Janisch T. Declining malaria parasite prevalence and trends of asymptomatic parasitaemia in a seasonal transmission setting in North-Western Burkina Faso between 2000 and 2009–2012. Malaria J. 2013;12(1):27. http://www.malariajournal.com/content/12/1/27
28. González-Scarano F, Martín-García J. The neuropathogenesis of AIDS. Nat Rev Immunol. 2005;5(1):69–81. Nature Publishing Group.
29. Halliday KE, Karanja P, Turner EL, Okello G, Njagi K, Dubeck MM, Allen E, Jukes MCH, Brooker SJ. Plasmodium falciparum, anaemia and cognitive and educational performance among school children in an area of moderate malaria transmission: baseline results of a cluster randomized trial on the coast of Kenya. Trop Med Int Health. 2012;17(5). Blackwell Publishing Ltd:532–49. doi:10.1111/j.1365-3156.2012.02971.x.
30. Hoare J, Fouche J-P, Spottiswoode B, Donald K, Philipps N, Bezuidenhout H, Christine M, Webster V, Oduro C, Schrieff L. A diffusion tensor imaging and neurocognitive study of HIV-positive children who are HAART-Naïve 'slow progressors'. J Neurovirol. 2012;18(3):205–12. Springer.

31. Holding PA, Stevenson J, Peshu N, Marsh K. Cognitive sequelae of severe malaria with impaired consciousness. Trans R Soc Trop Med Hyg. 1999;93(5):529–34.
32. Idro R, Karamagi C, Tumwine J. Immediate outcome and prognostic factors for cerebral malaria among children admitted to Mulago Hospital, Uganda. Ann Trop Paediatr. 2004;24(1):17–24. doi:10.1179/027249304225013240. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15005962
33. Idro R, Jenkins NE, Newton CR. Pathogenesis, clinical features, and neurological outcome of cerebral malaria. Lancet Neurol. 2005;4(12):827–40. S1474-4422(05)70247-7 [pii] doi:10.1016/S1474-4422(05)70247-7. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16297841
34. Idro R, Marsh K, John CC, Newton CR. Cerebral malaria: mechanisms of brain injury and strategies for improved neurocognitive outcome. Pediatr Res. 2010;68(4):267–74. doi:10.1203/PDR.0b013e3181eee738.
35. Jeremy RJ, Kim S, Nozyce M, Nachman S, McIntosh K, Pelton SI, Yogev R, et al. Neuropsychological functioning and viral load in stable antiretroviral therapy-experienced HIV-infected children. Pediatrics. 2005;115(2):380–87. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15687448
36. John CC, Bangirana P, Byarugaba J, Opoka RO, Idro R, Jurek AM, Wu B, Boivin MJ. Cerebral malaria in children is associated with long-term cognitive impairment. Pediatrics. 2008;122(1):e92–9. doi:10.1542/peds.2007-3709. peds.2007-3709 [pii].
37. John CC, Panoskaltsis-Mortari A, Opoka RO, Park GS, Orchard PJ, Jurek AM, Idro R, Byarugaba J, Boivin MJ. Cerebrospinal fluid cytokine levels and cognitive impairment in cerebral malaria. Am J Trop Med Hyg. 2008;78(2):198–205. 78/2/198 [pii].
38. John CC, Kutamba E, Mugarura K, Opoka RO. Adjunctive therapy for cerebral malaria and other severe forms of plasmodium falciparum malaria. Expert Rev Anti Infect Ther. 2010;8(9):997–1008. doi:10.1586/eri.10.90.
39. Jukes MC, Pinder M, Grigorenko EL, Smith HB, Walraven G, Bariau EM, Sternberg RJ, et al. Long-term impact of malaria chemoprophylaxis on cognitive abilities and educational attainment: follow-up of a controlled trial. PLoS Clin Trials. 2006;1(4):e19. doi:10.1371/journal.pctr.0010019. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17013430
40. Kihara M, Carter JA, Newton CR. The effect of plasmodium falciparum on cognition: a systematic review. Trop Med Int Health. 2006;11(4):386–97. doi:10.1111/j.1365-3156.2006.01579.x. TMI1579 [pii].
41. Kihara M, Carter JA, Holding PA, Vargha-Khadem F, Scott RC, Idro R, Fegan GW, de Haan M, Neville BG, Newton CR. Impaired everyday memory associated with encephalopathy of severe malaria: the role of seizures and hippocampal damage. Malar J. 2009;8:273. doi:10.1186/1475-2875-8-273. 1475-2875-8-273 [pii].
42. Kihara M, de Haan M, Garrashi HH, Neville BG, Newton CR. Atypical brain response to novelty in rural African children with a history of severe falciparum malaria. J Neurol Sci. 2010;296(1–2):88–95. S0022-510X(10)00219-4 [pii] doi:10.1016/j.jns.2010.05.018. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20566207
43. Kimbi HK, Nformi D, Ndamukong KJ. Prevalence of asymptomatic malaria among school children in an urban and rural area in the Mount Cameroon region. Cent Afr J Med. 2005;51(1–2):5.
44. Klingberg T, Fernell E, Olesen PJ, Johnson M, Gustafsson P, Dahlstrom K, Gillberg CG, Forssberg H, Westerberg H. Computerized training of working memory in children with ADHD – a randomized, controlled trial. J Am Acad Child Adolesc Psychiatry. 2005;44(2):177–86. S0890-8567(09)61427-1 [pii]. doi:10.1097/00004583-200502000-00010. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15689731
45. Laughton B, Cornell M, Grove D, Kidd M, Springer PE, Dobbels E, van Rensburg AJ, Violari A, Babiker AG, Madhi SA. Early antiretroviral therapy improves neurodevelopmental outcomes in infants. AIDS. 2012;26(13):1685–90. LWW.

46. Lozoff, B. Early iron deficiency has brain and behavior effects consistent with dopaminergic dysfunction. J Nutr. 2011;141(4):740S–746S. doi:10.3945/jn.110.131169. http://jn.nutrition.org/content/141/4/740S.abstract
47. McGrath N, Fawzi WW, Bellinger D, Robins J, Msamanga GI, Manji K, Tronick E. The timing of mother-to-child transmission of human immunodeficiency virus infection and the neurodevelopment of children in Tanzania. Pediatr Infect Dis J. 2006;25(1):47–52. http://journals.lww.com/pidj/Fulltext/2006/01000/The_Timing_of_Mother_to_Child_Transmission_of.12.aspx
48. Msellati P, Lepage P, Hitimana D-G, Van Goethem C, Van de Perre P, Dabis F. Neurodevelopmental testing of children born to human immunodeficiency virus type 1 seropositive and seronegative mothers: a prospective cohort study in Kigali, Rwanda. Pediatrics. 1993;92(6):843–8. Am Acad Pediatrics.
49. Murphy SC, Breman JG. Gaps in the childhood malaria burden in Africa: cerebral malaria, neurological sequelae, anemia, respiratory distress, hypoglycemia, and complications of pregnancy. Am J Trop Med Hyg. 2001;64(1–2 Suppl):57–67.
50. Nankabirwa J, Wandera B, Kiwanuka N, Staedke SG, Kamya MR, Brooker SJ. Asymptomatic plasmodium infection and cognition among primary schoolchildren in a high malaria transmission setting in Uganda. Am J Trop Med Hyg. 2013;88(6):1102–8. doi:10.4269/ajtmh.12-0633.
51. Nankabirwa JI, Wandera B, Amuge P, Kiwanuka N, Dorsey G, Rosenthal PJ, Brooker SJ, Staedke SG, Kamya MR. Impact of intermittent preventive treatment with dihydroartemisinin-piperaquine on malaria in Ugandan schoolchildren: a randomized, placebo-controlled trial. Clin Infect Dis. 2014;58(10):1404–12. Oxford University Press, ciu150.
52. Olney DK, Pollitt E, Kariger PK, Khalfan SS, Ali NS, Tielsch JM, Sazawal S, et al. Young Zanzibari children with iron deficiency, iron deficiency anemia, stunting, or malaria have lower motor activity scores and spend less time in locomotion. J Nutr. 2007;137(12):2756–62.
53. Opoka RO, Bangirana P, Boivin MJ, John CC, Byarugaba J. Seizure activity and neurological sequelae in Ugandan children who have survived an episode of cerebral malaria. Afr Health Sci. 2009;9(2):75–81. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19652740
54. Ruel TD, Boivin MJ, Boal HE, Bangirana P, Charlebois E, Havlir DV, Rosenthal PJ, et al. Neurocognitive and motor deficits in HIV-infected Ugandan children with high CD4 cell counts. Clin Infect Dis. 2012. cir1037 [pii] doi:10.1093/cid/cir1037. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22308272
55. Thuilliez J, Sissoko MS, Toure OB, Kamate P, Berthélemy JC, Doumbo OK. Malaria and primary education in Mali: a longitudinal study in the village of Donéguébougou. Soc Sci Med. 2010;71(2):324–34. doi:10.1016/j.socscimed.2010.02.027.
56. Van Rie A, Mupuala A, Dow A. Impact of the HIV/AIDS epidemic on the neurodevelopment of preschool-aged children in Kinshasa, democratic Republic of the Congo. Pediatrics. 2008;122(1):e123.
57. Van Rie A, Dow A, Mupuala A, Stewart P. Neurodevelopmental trajectory of HIV-infected children accessing care in Kinshasa, democratic republic of Congo. J Acquir Immune Defic Syndr. 2009;52(5):636–42. doi:10.1097/QAI.0b013e3181b32646. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19730268
58. White NJ, Pukrittayakamee S, Hien TT, Faiz MA, Mokuolu Oa, Dondorp AM. Malaria. Lancet. 2014. 383(9918):723–35. doi:10.1016/S0140-6736(13)60024-0. http://www.ncbi.nlm.nih.gov/pubmed/23953767

Chapter 13
Acquired Brain Injury in Children in Sub-Saharan Africa

Richard Idro

Abstract The World Health Organization estimates that the proportionate share of the total global burden of disease resulting from neurologic and psychiatric disorders will rise to 14.7 % by 2020. Although these disorders comprise only 1.4 % of all deaths, they account for a remarkable 28 % of all years of life lived with a disability. In Africa, brain injury acquired during childhood underlies the majority of the neurologic disorders. There are however very few comprehensive studies of these on the continent. Available studies are mostly of specific etiologies and often conducted in localized areas. This chapter provides an overview of traumatic and acquired non-traumatic brain injury in children in sub-Saharan Africa. It highlights the burden, causes, manifestations and management challenges and provides some perspectives for the future. The chapter will deal with only acquired brain injury in children after birth in sub-Saharan Africa. Genetic disorders and disorders due to early adverse foetal exposures are not included here.

Keywords Mental, neurological and substance abuse disorders • Traumatic and non traumatic acquired brain injury • Either children or childhood • Burden of disease • Sub Saharan Africa

Traumatic Brain Injury

Traumatic brain injury (TBI) is a major factor in the high burden of the acquired neurologic and psychiatric disorders worldwide [1]. The incidence is rising mainly due to injuries arising from the increased use of motor vehicles, especially in low and middle-income countries. The incidence in Europe is 235 per 100,000 per year [2]. Although reliable data is scarce, the burden in sub-Saharan Africa is thought to be much higher. In Johannesburg, South Africa, for example, the incidence was estimated at 316 per 100,000 per year [3]. In Nigeria in a 5 year prospective study of paediatric head trauma, one centre in Nigeria that treated 13 % of cases in its catchment area documented

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S. Musisi, S. Jacobson (eds.), *Brain Degeneration and Dementia in Sub-Saharan Africa*, DOI 10.1007/978-1-4939-2456-1_13

127 cases (65 male and 62 female) [4]. The median age was 7 years (range 3 months to 17 years) with peak incidence in the age group 6–8 years. Motor vehicle injuries were the major cause (67.7 %), followed by falls (14 %) and then violence (7 %). The most frequent computed tomography scan finding was an intra cerebral hemorrhage. The median duration of hospitalization was 11 days. Eleven patients (8.7 %) died and mortality increased with worsening severity of brain injury and the presence of intracerebral hematoma [4]. A similar study over the same duration in South Africa also documented a peak incidence at 6 years. The major mechanism of injury was pedestrian road traffic accidents. In the South African centre however, more males than females were affected and most injuries occurred over the weekends [5].

Severe TBI in Africa is however not only a concern for urban centres but also rural areas. The etiology in the two areas may be different. In a study that compared 248 admissions with head injury to one rural hospital in Tanzania and 432 patients at an urban centre in the same country, the prevalence of TBI was significantly higher in the rural area compared to the urban area (34.2 % vs. 21.9 %). TBI due to violence was more frequent in the rural area whereas road traffic accidents were more frequent at the urban centre. Injuries in rural areas were also more severe: the number of patients with a normal brain CT imaging was significantly higher in the urban area compared to the rural area (53.0 % vs. 35.9 %). Bone fractures (35.9 % vs. 15.7 %) and pneumocephalus (6.9 % vs. 0.9 %) were also documented more frequently in the rural centre [6]. The differences in etiology, burden and severity of TBI between urban and rural areas of Africa demonstrate that patients with severe TBI are not a primarily urban concern but that both rural and urban centres should develop capacity to offer care for acute TBI.

In countries such as Uganda, there is an epidemic of motorcycle related injuries. These vehicles, mostly motor cycle taxis also called *boda boda,* are a cheap and ubiquitous form of transport in both urban and rural areas of the country and are often ridden by ill-trained young men who rarely use helmets. Their passengers often don't also wear helmets. Here, *boda boda* injuries are so common that in one referral hospital, up to 70 % of the trauma surgery resource was spent on them. A police report in the Daily Monitor, a local daily newspaper, of January 14 2012, stated that up to 40 % of serious road accidents and crashes involving *boda boda* cyclists were fatal. An organised transport system and implementation of strict safety procedures is imperative if this epidemic is to be managed.

In terms of acute care provision, neurosurgical interventions and brain imaging capacity is available in only a few urban centres and therefore most patients receive less than optimum care. As management capacity improves, the care of patients with TBI should be included in the training curricula for all health personnel irrespective of whether their workplace is primarily urban or rural [6].

Non-traumatic Brain Injury

One of the earliest descriptions of childhood neurologic disorders in Africa was a study of 138 Ugandan children attending an outpatient clinic in early 1970s [7]. In this study, Egdell and Stanfield observed that the majority of patients had a

postnatal onset of symptoms often following a catastrophic febrile illness. A significant proportion also had neonatal symptom onset with history of an abnormal birth, a history of abnormal neurology dating from birth or both. The authors concluded that in this region, primary prevention of early childhood brain injury and neurologic disease should focus on early diagnosis and treatment of cerebral malaria, bacterial meningitis and viral encephalitis and on improved obstetric care. Similar findings remain to date [8].

Neonatal Brain Injury

In low and middle income countries, birth is the time of highest risk for brain injury and death [9]. The 2.9 million annual neonatal deaths worldwide have been attributed to three main causes: intrapartum conditions including neonatal encephalothy (hypoxic ischemic encephalopathy and bilirubin encephalopathy, 0.7 million), severe neonatal infections including neonatal meningitis (0.6 million) and complications of preterm delivery such as hypoglycemia, hypothermia, intraventricular hemorrhage (1.0 million). The contribution of metabolic causes is undetermined mostly because of limited data. Boys have a higher biological risk of neonatal death, but girls often have a higher social risk.

Low birth weight due to prematurity, small-for-gestational-age (SGA), or both, is the biggest risk factor [9]. Although South Asia has the highest rates of SGA, sub-Saharan Africa has the highest rates for preterm birth. Term SGA babies have an increased risk of stunting and adult-onset metabolic conditions. Preterm births, especially those younger than 32 weeks' gestation, are at the highest risk of neonatal death, post-neonatal mortality, and long-term neuro-developmental impairments (Fig. 13.1).

Neonatal sepsis causes over 25 % of all neonatal deaths in the continent [10]. This number is probably an underestimate as reliable data is limited. Mortality is over 30 % in babies with invasive bacterial disease. In one centre in Kenya, a wide range of bacteria were isolated in out-of-hospital born babies including Klebsiella spp., Staphylococcus aureus, Streptococcus pneumoniae, Group B Streptococcus, Acinetobacter spp., Escherichia coli, and Group A Streptococcus [11]. In this region of Kenya, 9 % of neonates admitted to hospital had seizures with the incidence of neonatal seizures being 39.5 [95 % CI 26.4–56.7] per 1000 live-births. The main diagnoses in neonates with seizures was sepsis (60 %), neonatal encephalopathy (21 %) and meningitis (15 %) [12].

Several large community-based epidemiologic and hospital studies confirm neonatal birth injury as a leading cause of long term disability in Africa. In Kenya, in a survey of 10,218 children, the prevalence of moderate and severe impairment was 61 per 1,000 [95 % CI 48–74]. The most common domains affected were epilepsy (41/1,000), cognition (31/1,000), and hearing (14/1,000). Neonatal insults were the single most important risk factor for impairment [8]. Again, in the largest study of epilepsy in sub-Saharan Africa that surveyed over 500,000 individuals in Ghana, South Africa, Tanzania, Kenya and Uganda, again the most important risk

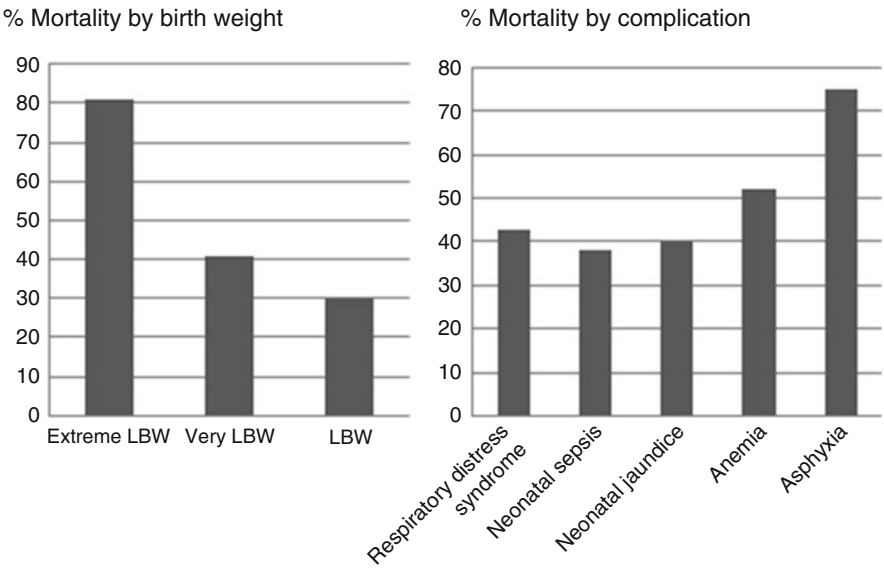

Fig. 13.1 Short-term outcomes of low-birth-weight (LBW) neonates in Kilifi District Hospital, Kenya, 2003–2004

factors were difficulties at birth or an abnormal antenatal period [13]. The conclusion from these studies is that programs to improve antenatal and perinatal care could substantially reduce the prevalence of epilepsy in the region.

In recent days, there have been heightened interventions by governments, international and local non-governmental organizations to improve neonatal outcomes in the region. Major programs in sub-Saharan Africa have included simple interventions to prevent intrapartum complications (e.g. prevention and management of pre-eclampsia), detect and manage intrapartum problems (e.g. monitoring progress of labor with access to emergency obstetric care), and the identification and assisted breathing for the non-breathing newborn babies [14]. Other interventions include community-based strategies to increase skilled birth attendance, the use of the partograph by frontline health workers linked to emergency obstetric care, task shifting to increase access to Cesarean delivery and the "helping babies breathe" program. The "helping babies breathe program" – a train the trainers course for the provision of neonatal resuscitation in resource poor settings – is one of the leading interventions [15]. Evaluation of the program in Rwanda, Ethiopia and Tanzania suggest that this program together with the other interventions have potential to significantly improve both short and long term neonatal outcomes in the region [16–18].

Brain Injury in Childhood

Central nervous system infections in childhood are the other leading cause of brain injury and neuro-disability on the continent [19]. The most important of these are cerebral malaria, bacterial meningitis, and viral meningitis or meningo-encephalitis [20].

Table 13.1 Acute infectious encephalopathies in children in one of four general pediatric wards in Mulago hospital, Kampala, Uganda, 2006–2008

Acute infectious encephalopathy	Overall number of patients	Median (IQR) age (months)	Inpatient mortality (%)
Cerebral malaria	87	36 (18–69)	12
Acute bacterial meningitis	81	8 (3–29)	18
Encephalopathy of undetermined aetiology, probably viral encephalitis	13	48 (27–96)	30
Total	181	24 (7–69)	16

Table 13.1 shows the distribution of these encephalopathies in a general paediatric ward of Mulago, the teaching hospital for Makerere University College of Health Sciences in Uganda (reference).

All three are associated with high mortality and a significant proportion of survivors have neurological and cognitive sequelae [21, 22]. Other central nervous systems infections include tuberculous meningitis, multiple parasitic infections, primary HIV disease and HIV associated opportunistic infections and stroke especially from sickle cell anaemia. Increasingly, drug and substance abuse disorders are also becoming a problem especially in teenagers in who, the risk of injury is further compounded by reckless exposure to potentially traumatic events.

Bacterial Meningitis

The peak incidence of bacterial meningitis in sub-Saharan Africa is in the first year of life and the leading etiologies include *Haemophilus influenza* type b, pneumococcus, non-typhi salmonella (more prevalent in HIV infected individuals) and other gram negative bacteria and epidemics of type C meningococcal meningitis.

Despite a reported decline in numbers especially since the introduction of the conjugate *Haemophilus influenzae* type b vaccine [23, 24], one third of children with bacterial meningitis still die and over 25 % are left with severe sequelae [21, 25–27]. The main pathophysiological mechanism is meningeal inflammation. Bacterial cell wall antigens activate an acute inflammatory process in the subarachnoid space producing oxidant stress and inflammatory injury to neurons [28–30]. Infection may extend into the labyrinth and cause sensori-neural deafness [31] or along penetrating vessels causing a vasculitis. Involvement of the vascular intima may obliterate vessels and cause necrosis of brain tissue. Infarcts may be limited to one vessel or involve large cortical areas resulting into hemiparesis or quadriparesis and subsequently, epilepsy and learning disability [32–35]. Acute hydrocephalus and brain swelling worsen intracranial hypertension, which reduces cerebral perfusion further leading to ischemic injury [35, 36].

There are several patient management challenges that affect the treatment of bacterial meningitis in Africa. These include misdiagnosis (in many malaria endemic areas, the default position for many clinicians is to treat a febrile illness in a child

with an anti malarial), delayed presentation and therefore late initiation of specific antibiotic therapy and a growing problem of multiple drug resistance with indiscriminate antibiotic use. Thus, although intravenous ceftriaxone, 100 mg/kg/day is first line therapy in many centres, there are reports of drug resistance and treatment failures yet, alternative treatments are few. Furthermore, adjuvant therapy with steroids which has been shown to improve outcome elsewhere has not shown similar benefits in Africa probably because of the high burden of HIV/AIDS or exposure to antibiotics prior to presentation [37]. Upon recovery, follow up care and rehabilitation is almost non-existent in most centres. Thus, the long-term outcome of bacterial meningitis in the region remains poor.

Cerebral Malaria

Malaria is a major cause of ill health, neurodisability and death in tropical countries. Most transmission occurs in sub-Saharan Africa and in South East Asia. In 2010, the World Health Organization estimated that there were 216 million clinical cases of malaria and 655,000 deaths. Most of the deaths occurred in Africa among children younger than 5 years. Here, the incidence of disease is lower and less severe in the older children and adults most probably, as a result of the building immunity [38]. Recent reports suggest that the incidence of malaria is on the decline in many endemic countries [39, 40].

The manifestations of *P. falciparum* range from asymptomatic parasitemia to severe and fatal disease. The majority of clinical infections are mild or uncomplicated. Patients have fever, headache, chills, and body aches. Approximately 1 % of patients with uncomplicated clinical infection go on to develop severe complications of disease and present with severe malaria. Severe malaria is defined by clinical or laboratory evidence of vital organ dysfunction, usually in association with asexual parasitemia. Severe malaria may manifest with prostration, repeated seizures, shock, jaundice, abnormal bleeding, prostration, impaired consciousness or coma, severe anemia, hypoglycemia, metabolic acidosis, acute kidney injury, or multiple organ failure and is associated with greater than 5 % mortality. Among African children, the syndromes of severe malaria anemia, malaria with respiratory distress and malaria with impaired consciousness or coma (cerebral malaria) encompass the majority of presentations and most severe disease.

Cerebral malaria is a diffuse encephalopathy characterized by parasite sequestration in post capillary venules as a consequence of adherence of infected erythrocytes to the endothelial cell lining [41]. Diagnosis is made in a patient with peripheral malaria parasitemia, unrousable coma and no other cause to explain the coma [41]. Brain injury probably results from hypoxic or inflammatory injury initially affecting the cerebral micro-vascular endothelium [42]. The sequestered mass reduces blood flow and alters blood-brain barrier function but without significant leakage of plasma proteins into perivascular spaces [43]. Changes in blood brain barrier function may be a result of minute disruptions in endothelial junctions [43, 44].

Blood brain barrier dysfunction may contribute to intracranial hypertension [45, 46]. However, increased cerebral blood volume following sequestration and increased blood flow in seizures, hyperthermia and anemia may better explain the increased intracranial pressure [47, 48]. A critical reduction in metabolite supply may occur but significant neural necrosis is unlikely since with anti malaria treatment, coma is reversible. However, during periods of increased metabolic demand (e.g. during seizures), the risk of neural injury is high and is worse in patients with hypoglycemia [49] or when blood flow is further compromised by intracranial hypertension [46]. Many with severe intracranial hypertension die or survive with sequelae [50]. Thus, sequelae have been associated with prolonged and repeated seizures, deep and prolonged coma, intracranial hypertension and hypoglycemia [51].

In cerebral malaria, 15–20 % die and 25 % have persistent neurologic, cognitive and behavioral impairments or epilepsy [41, 52, 53]. These impairments affect the child's development and quality of life, placing an economic and social burden on families that often have limited resources. Supportive therapy may improve outcome, but trials of adjunct therapies have been disappointing.

Viral Encephalitis

Viral infections of the central nervous system are an important cause of hospitalization and death in children in sub-Saharan Africa. Etiology is diverse. In a study of 513 Malawian children with suspected central nervous system viral infections from 2002 to 2004, at least one virus was detected in 133 children (26 %) of whom, 43 (33 %) died. Twelve different viruses were detected. Adenovirus was the most common infection, affecting 42 children. Mumps, human herpes virus 6, cytomegalovirus, herpes simplex virus 1 and enterovirus were also important. These infections were as important even among children whose coma was attributably solely to cerebral malaria [54]. Forty five (9 %) of the 513 children had both *plasmodium falciparum* parasitemia and viral infection, including 27 (35 %) of 78 diagnosed clinically with cerebral malaria. Children with dual infection were more likely to have seizures than those with malaria parasitemia alone, viral infection only, or neither. Seventeen children (38 %) of the 45 children with dual infection died, compared with 26/88 (30 %) with viral infection only, 17/118 (14 %) of parasitemia only, and 34/262 (13 %) with neither. This and a second study in Kenya [55] suggested that interaction between viral central nervous system infections and malaria parasitemia could increase disease severity.

Rabies is an important problem in urban centres. The clinical manifestations may be unusual and diagnosis may be made at post-mortem. In the Malawi series, 3/26 (11.5 %) of 26 fatal cases were mistakenly originally attributed to be cerebral malaria [56].

Brain injury in viral encephalitis is caused by either direct (primary) or indirect (post-infectious) involvement of brain tissue. In primary disease, viruses replicate in neurons, glia or macrophages, both in white and grey mater. In herpes encephalitis,

there is necrosis of brain tissue with hemorrhage and softening and in severe cases, extensive loss of neurons. Mortality is high and among surviving patients, long-term moderate to severe sequelae develop in up to 35 %. These include hemi-paresis, epilepsy, aphasia and behavioral problems [57–59].

Of the three encephalopathies, the diagnosis and management of viral encephalitis is least developed in Africa. Laboratory capacity (e.g. for PCR diagnosis) is poor and very few centers have the diagnostic capacity to offer appropriate management. Thus, the provision of specific treatment even for etiologies for which specific drug therapies are available, such as herpes simplex encephalitis, still has a long way to go.

HIV/AIDS

In 2012, the World Health Organization estimated that over 90 % of the approximately 3.4 million children with human immunodeficiency virus worldwide were in sub-Saharan Africa. Most paediatric HIV disease is vertically acquired through mother-to-child transmission and many patients are not on antiretroviral therapy (ART) [60]. The neurological complications of HIV-1 can be divided into those due to direct HIV-1 infection of the brain (primary disorders such as HIV encephalopathy) or due to indirect complications (opportunistic infections and malignancies). In addition, children infected with HIV are also at risk of other CNS disorders unrelated to the underlying infection.

HIV encephalopathy is the hallmark of untreated primary HIV infection of the brain. It presents with a triad of acquired microcephaly, neurodevelopmental delay and progressive motor dysfunction that are not attributable to other biological and environmental risk factors. This is a clinical consequence of early HIV invasion of the developing fetal and infant brain and characteristically presents in infancy and in toddlers. The commonest neurologic findings are a global developmental delay or regression together with pyramidal tract signs and seizures. The presentation differs according to age and mode of HIV-1 infection. Infants and younger children manifest the most severe and global dysfunction, a smaller head circumference, and lower birth weight, while older children have more specific signs. In one series, the mean head circumference was below the third percentile in 40 % of HIV-infected compared with 22 % of uninfected children [61]. The encephalopathy can be progressive with loss of acquired skills or stagnation/plateau in attaining developmental milestones or static in which case the children acquires new skills and abilities more slowly than normal. Their standardised test scores are below average, but stable. HIV infected children may also develop other mental and cognitive deficits evident at different ages [62]. Behavioral problems are more common in preschool and school aged children while focal seizures are more common in older children and pre-adolescents. Rapid progression of the disease carries a grave prognosis [63].

Other manifestations of HIV nervous system disease include stroke, myelopathies, peripheral neuropathy, myopathy, epilepsy, CNS lymphomas and neuropsychiatric

difficulties including Attention Deficit Hyperactivity Disorders, ADHD. Stroke is the most common cause of focal neurological deficits. This may be a direct result of HIV infection, may be secondary to opportunistic infections or HIV arteriopathy. Adolescents with long standing disease may also develop accelerated atherosclerotic cerebrovascular disease. Thus, management of stroke in these children should include low-dose aspirin administration [64]. Epilepsy may be a direct consequence of HIV infection or may be an acquired pathology. Because of its limited drug to drug interactions with most antiretroviral medications, sodium valproate is suggested as the first line anti-epileptic drug. The second line drug is lamotrigine. Structural cord lesions must be excluded in children presenting with paraparesis. Peripheral neuropathy and myopathies are often compounded by antiretroviral therapy. Other manifestations of central nervous system involvement and brain injury in HIV/AIDS include progressive multifocal leukoencephalopathy (PML) [65].

Brain imaging in HIV encephalopathy shows cortical cerebral atrophy with dilatation of the lateral ventricles and calcification of the basal ganglia and, periventricular involvement of the white matter [63]. These changes may predate neurological deterioration. Patients may show clinical, cognitive and functional improvement or plateauing of symptoms with initiation of highly active antiretroviral therapy (HAART), although abnormal neurological signs and gross motor difficulties persist [66]. The non-nucleoside reverse transcriptase inhibitors such as nevirapine have the best potential for treatment of CNS disease because of CNS penetration [67]. Differences in the effects on cognitive function in different settings may be a result of infection by different HIV clades [68]. Micronutrient deficiencies may worsen outcomes [69]. The long term preventive strategy should be interventions to prevent HIV/AIDS.

Tuberculous Meningitis

In 2007, the World Health Organization estimated that there were 9.27 million new clinical cases of *mycobacterium tuberculosis* (139/100,000) and 13.7 million prevalent cases (206/100,000). Most patients have pulmonary tuberculosis (TB). Central nervous system involvement, one of the most devastating clinical manifestations of TB, accounts for 5–10 % of extrapulmonary cases, and for 1 % of all TB cases. The HIV/AIDS epidemic has ballooned the problem. Today, 1.4 million new cases of TB occur in HIV infected individuals annually [70] and TB also accounts for 23 % of AIDS related deaths.

Tuberculous meningitis (TBM) is the most severe complication of *Mycobacterium tuberculosis* infection. The peak incidence is in childhood where it is associated with very high morbidity and mortality. Most patients report non-specific symptoms (including malaise, anorexia, fatigue, fever, myalgias, and headache), that last 2–8 weeks prior to the development of signs of meningitis. Due to the non-specific nature of the early symptoms, in many hospitals, a diagnosis of TBM is considered after considerable neurological damage has already occurred.

Childhood TBM usually develops within 3 months of primary TB infection [71]. A family history of TB is common. Most patients present with fever. Neurological features range from lethargy, stiff neck, seizures, agitation or coma. Cranial nerve palsies are common and may be the presenting manifestation. Fundoscopy may show papilloedema and choroid tubercles especially in patients in who TBM is associated with miliary tuberculosis [72]. Clinically, the degree of neurological involvement and extent of brain injury correlates with stages of the contemporary modification [73] of the Medical Research Council Staging of TBM. These stages are:

I. Alert and oriented without focal neurological deficits
II. Glasgow coma Score of 4–11 or 15 with focal neurological deficits
III. Glasgow coma score of 10 or less, with or without focal neurological deficits

Cerebrovascular complications typically involve regions supplied by the middle cerebral artery and its perforating branches. These lesions may be a consequence of local inflammatory exudates which may also trap the cranial nerves. Infiltrative, proliferative and necrotising vessel pathologies may lead to luminal thrombosis and single or multiple infarcts. The brain CT scan can help diagnose TBM, and is useful in decisions regarding surgical interventions for hydrocephalus. Choroid plexus enhancement with ventricular enlargement on imaging is highly suggestive of TBM. The MRI shows diffuse, thick, meningeal enhancement. Cerebral infarcts can be seen in nearly 30 % of cases [74].

The first-line treatment regiment for TBM is a combination of daily Isoniazid, Rifampicin, Pyrazinamide and Ethambutol. The most important determinant of outcome is the stage at which treatment is started. Other determinants include age, malnutrition, hydrocephalus and focal neurological deficits. Mortality and morbidity is low in stage I disease but in stage III almost 50 % of patients die. Survivors manifest a variety of neurological sequelae [75].

Other forms of central nervous system involvement include intracranial TB such as TB encephalopathy, vasculopathy, tuberculoma and brain abscess or spinal forms such as Pott's disease, non-osseous spinal tuberculoma and spinal meningitis.

Nodding Syndrome

Nodding syndrome is a poorly understood but devastating chronic brain disorder affecting thousands of individuals in the eastern African countries of South Sudan, Uganda and Tanzania [76]. There are reports of possible cases in west (Liberia) and central Africa (Burundi and the Democratic Republic of Congo). In Tanzania, nodding syndrome has affected a relatively smaller number of individuals. The picture in South Sudan and northern Uganda is that of an epidemic. The World Health Organization recently classified nodding syndrome under the neglected tropical diseases [80]. Clinical studies suggest that it may be an epileptic encephalopathy and probably symptomatic generalised epilepsy disorder [76–79]. The syndrome affects previously normally developing children. Symptoms develop between the ages of

3–15 years [78, 80]. Head nodding, the pathognomonic feature is an atonic seizure [78]. Over the years, this is complicated by frequent tonic clonic, myoclonic and atypical absence seizures, declining cognitive and motor function, psychiatric disorders, wasting, growth failure and physical deformities leading to severe disability and in some cases death. These complications develop through five clinical stages of a prodrome, head-nodding, multiple seizures and severe disability. These time intervals may potentially provide windows for intervention to arrest progression.

The background electroencephalogram (EEG) is characterised by generalised slow wave activity and multiple inter-ictal epileptiform discharges. Ictal EEG activity consists of mostly generalised spike and spike and wave discharges. Brain imaging shows generalised cerebral and cerebellar cortical atrophy [76–78].

A number of toxic, nutritional, infectious, para-infectious and environmental causes have been studied but to date, there have been no leads except an epidemiologic association with O. volvulus (reviewed in [81]). Testing for 19 virus families has been negative. The affected age group and duration of symptoms makes prion disease unlikely. The EEG and brain MRI too are uncharacteristic [76, 77]. Clustering of cases within specific locations and within families suggest a common exposure [77]. The affected communities are not known for consanguineous marriages and no specific epilepsy genes were identified on exon sequencing in two children [81]. In south Sudan, 76 % of cases and 47.4 % controls had O. volvulus microfilaria on skin snip testing [82], while in Uganda, 94.9 % cases and 48.8 % controls tested positive for O. volvulus specific antibodies [83]. However, O. volvulus is endemic in many parts of Africa, Latin America and Asia, yet nodding syndrome has only been reported in a few areas. Also, it is unclear how the parasites would cause brain injury as there is no evidence of breach of blood brain barrier [76]. Alternative mechanisms other than direct parenchymal injury are likely.

Using proteomics, American investigators at the Centers of Disease Control and the National Institutes of Health have demonstrated antibodies against leiomodin-1 (a muscle protein also expressed in neurons) in 11/19 (58 %) cases. Part of this protein shares 83 % sequence similarity with a conserved region of *O. volvulus* tropomyosin. The antibodies were neuro-toxic in mice brain suggesting that neuropathology in nodding syndrome may be caused by cross-reacting antibodies (Tory Johnson et al., unpublished). Separately, we studied serum samples of 31 patients and 11 sibling controls for antibodies against the neuron surface protein – voltage-gated potassium channel (VGKC) complex proteins and against the intracellular glutamic acid decarboxylase (*GAD*); 15/31(48.3 %) cases and 1/11(9.1 %) controls had antibodies against the VGKC but none tested positive for antibodies against the intracellular GAD, (Richard Idro, unpublished). These pilot studies await confirmation. Other than *O. volvulus*, another source of cross-reacting antibodies may be host response to variant *Wolbachia* species which are essential symbiotic bacteria of filarial worms. Again, further studies are awaited.

There is currently no specific treatment for nodding syndrome. The only available treatment is a cocktail of symptomatic therapies we developed and includes sodium valproate for seizures, nutritional, behavior and physical therapy [84]. Because of the strong epidemiological association with *O. volvulus,* all individuals

living within the nodding syndrome belt also receive twice yearly doses of ivermectin. Ivermectin kills microfilaria but hardly has any effect on the adult parasite. Instead, these continue to produce microfilaria and may do so for a lifespan lasting 5–15 years. Why Nodding Syndrome reached epidemic proportions during wartime in Uganda with no new cases reported after cessation of hostilities and closure of IDP camps remains an unanswered question, but raises the question of the sequelae of childhood trauma in our African wars. Until definite treatments are obtained, the outlook for nodding syndrome remains poor.

Sickle Cell Anemia

Sickle cell anemia (SCA) is a public health priority. Annually, there are about 300,000 births and over 75 % of this is in Africa where SCA is a major cause of childhood deaths [85, 86]. SCA is characterized by a point mutation in position 6 of the β globin gene in which adenine is replaced by thymidine resulting in glutamic acid being replaced by valine. The majority of patients have the Hb SS genotype but Hb SC and Hb S/beta + thalassemia are also common in West Africa. The mutation alters the physical properties of hemoglobin so that in conditions of reduced oxygen tension, the sickle haemoglobin polymerizes altering the shape of the red blood to a sickle-like shape. The movement of red blood cells through the capillary bed is thus impaired clogging the system.

The commonest age of presentation is 1–3 years. Children present with anemic crises (hemolysis, splenic sequestration, folate deficiency, and possibly aplastic), painful and infarctive crises (hand-foot syndrome, bone-pain, pulmonary and abdominal) or acute infections (malaria, pneumonia, septicemia, meningitis, osteomyelitis), priapism or cardiovascular accidents resulting in severe morbidity and early mortality. The main causes of death include overwhelming systemic infections, sickle cell crises, and brain injury from acute stroke [87]. Genetic factors associated with a better prognosis include the Senegal haplotype (which has higher levels of Hb F), and presence of alpha + thalassemia. Among environmental factors of a better prognosis, the family is of proven importance [87].

Stroke, including asymptomatic cerebro-vascular events, is a significant cause of morbidity and mortality in SCA. The incidence is 10–25 per 100 cases a year. Studies suggest cerebral stenosis in the circle of Willis may be the most common mechanism of stroke in children. Clinically, this may be predicted by an increased cerebral blood flow and patients with blood flow velocities greater than 200 m/s are at high risk of a stroke. In patients suffering a stroke, imaging shows infarcts in the distribution of the affected vessel. Some may have had several small silent infarcts prior to a major event [88].

The mortality of SCA in the USA and UK has decreased from 3 down to 0.13 per 100 person years of observation with the implementation of simple interventions such as newborn screening. The absence of programs for early diagnosis, comprehensive care and prevention, lack of locally appropriate information and negligible

investment in care and research has hindered similar progress in Africa [85]. In a large prospective cohort of 1,725 Tanzanian patients recruited between 2004 and 2009, mortality was 1.9 (95% CI 1.5, 2.9) per 100 per person years of observation. Mortality was highest among children under 5-years old [7.3 (4.8–11.0) per person years of observation] suggesting that additional interventions are critical at this age [85]. However, even basic clinical interventions and follow up care can improve outcome. These programs should include malaria chemoprevention, immunisations and daily penicillin to prevent infections by capsulated organisms and screening for elevated blood flow velocity [89].

Conclusion: Future Perspectives

First, there is urgent need for comprehensive epidemiologic studies of causation and burden of patients with brain injury in sub-Saharan Africa. Secondly, both the acute mortality and deaths secondary to long term morbidity are very high. Rehabilitation needs are hardly known and skilled human resource to undertake the rehabilitation is rare in sub-Saharan Africa. There are only limited disability screening programs and rehabilitation services in the region. Standardized testing is clearly required to define deficits, compare outcomes in different centers and to monitor improvements. Clearly investments are needed for both primary prevention of brain injury and secondary prevention of disability. Studies are also required to define adequate recovery in Africa and to adapt tools to measure functioning in these children. In the meantime, task shifting may help. There is need to train frontline healthcare workers to provide basic rehabilitation services for the majority of patients and refer only complex patients. The family may also be involved in helping with say physiotherapy.

The population of Africa is growing rapidly and with improving acute care for severely ill children, the number surviving is increasing. Put together, we have, on our hands, a growing number of brain injured children at risk of long term disability. The demand on rehabilitation services can only increase. With limited resources, innovative care practices and education are urgently required. Stigma from the behavioral sequelae of TBI needs to be addressed within such programs.

References

1. Menken M, Munsat TL, Toole JF. The global burden of disease study: implications for neurology. Arch Neurol. 2000;57(3):418–20.
2. Tagliaferri F, Compagnone C, Korsic M, Servadei F, Kraus J. A systematic review of brain injury epidemiology in Europe. Acta Neurochir. 2006;148(3):255–68. Discussion 68.
3. Nell V, Brown DS. Epidemiology of traumatic brain injury in Johannesburg – II. Morbidity, mortality and etiology. Soc Sci Med. 1991;33(3):289–96.
4. Udoh DO, Adeyemo AA. Traumatic brain injuries in children: a hospital-based study in Nigeria. Afr J Paediatr Surg. 2013;10(2):154–9.

5. Schrieff LE, Thomas KG, Dollman AK, Rohlwink UK, Figaji AA. Demographic profile of severe traumatic brain injury admissions to Red Cross War Memorial Children's Hospital, 2006–2011. S Afr Med J (Suid-Afrikaanse tydskrif vir geneeskunde). 2013;103(9):616–20.
6. Maier D, Njoku Jr I, Schmutzhard E, Dharsee J, Doppler M, Hartl R, et al. Traumatic brain injury in a rural and an urban Tanzanian hospital – a comparative, retrospective analysis based on computed tomography. World Neurosurg. 2014;81(3–4):478–82.
7. Egdell HG, Stanfield JP. Paediatric neurology in Africa: a Ugandan report. Br Med J. 1972;1(5799):548–52.
8. Mung'ala-Odera V, Meehan R, Njuguna P, Mturi N, Alcock KJ, Newton CR. Prevalence and risk factors of neurological disability and impairment in children living in rural Kenya. Int J Epidemiol. 2006;35(3):683–8.
9. Lawn JE, Blencowe H, Oza S, You D, Lee AC, Waiswa P, et al. Every newborn: progress, priorities, and potential beyond survival. Lancet. 2014;384(9938):189–205.
10. Seale AC, Mwaniki M, Newton CR, Berkley JA. Maternal and early onset neonatal bacterial sepsis: burden and strategies for prevention in sub-Saharan Africa. Lancet Infect Dis. 2009; 9(7):428–38.
11. Talbert AW, Mwaniki M, Mwarumba S, Newton CR, Berkley JA. Invasive bacterial infections in neonates and young infants born outside hospital admitted to a rural hospital in Kenya. Pediatr Infect Dis J. 2010;29(10):945–9.
12. Mwaniki M, Mathenge A, Gwer S, Mturi N, Bauni E, Newton CR, et al. Neonatal seizures in a rural Kenyan District Hospital: aetiology, incidence and outcome of hospitalization. BMC Med. 2010;8:16.
13. Ngugi AK, Bottomley C, Kleinschmidt I, Wagner RG, Kakooza-Mwesige A, Ae-Ngibise K, et al. Prevalence of active convulsive epilepsy in sub-Saharan Africa and associated risk factors: cross-sectional and case-control studies. Lancet Neurol. 2013;12(3):253–63.
14. Wall SN, Lee AC, Carlo W, Goldenberg R, Niermeyer S, Darmstadt GL, et al. Reducing intrapartum-related neonatal deaths in low- and middle-income countries-what works? Semin Perinatol. 2010;34(6):395–407.
15. Steele C. Helping babies breathe around the world. J Obstet Gynecol Neonatal Nurs. 2013;42(2):243–6.
16. Hoban R, Bucher S, Neuman I, Chen M, Tesfaye N, Spector JM. 'Helping babies breathe' training in sub-Saharan Africa: educational impact and learner impressions. J Trop Pediatr. 2013;59(3):180–6.
17. Msemo G, Massawe A, Mmbando D, Rusibamayila N, Manji K, Kidanto HL, et al. Newborn mortality and fresh stillbirth rates in Tanzania after helping babies breathe training. Pediatrics. 2013;131(2):e353–60.
18. Musafili A, Essen B, Baribwira C, Rukundo A, Persson LA. Evaluating helping babies breathe: training for healthcare workers at hospitals in Rwanda. Acta Paediatr. 2013;102(1):e34–8.
19. Carter JA, Neville BG, Newton CR. Neuro-cognitive impairment following acquired central nervous system infections in childhood: a systematic review. Brain Res Brain Res Rev. 2003; 43(1):57–69.
20. Gwer S, Chacha C, Newton CR, Idro R. Childhood acute non-traumatic coma: aetiology and challenges in management in resource-poor countries of Africa and Asia. Paediatr Int Child Health. 2013;33(3):129–38.
21. Pelkonen T, Roine I, Monteiro L, Correia M, Pitkaranta A, Bernardino L, et al. Risk factors for death and severe neurological sequelae in childhood bacterial meningitis in sub-Saharan Africa. Clin Infect Dis. 2009;48(8):1107–10.
22. Anga G, Barnabas R, Kaminiel O, Tefuarani N, Vince J, Ripa P, et al. The aetiology, clinical presentations and outcome of febrile encephalopathy in children in Papua New Guinea. Ann Trop Paediatr. 2010;30(2):109–18.
23. Cowgill KD, Ndiritu M, Nyiro J, Slack MP, Chiphatsi S, Ismail A, et al. Effectiveness of Haemophilus influenzae type b conjugate vaccine introduction into routine childhood immunization in Kenya. JAMA. 2006;296(6):671–8.

24. Roca A, Bassat Q, Morais L, Machevo S, Sigauque B, O'Callaghan C, et al. Surveillance of acute bacterial meningitis among children admitted to a district hospital in rural Mozambique. Clin Infect Dis. 2009;48 Suppl 2:S172–80.
25. Molyneux E, Riordan FA, Walsh A. Acute bacterial meningitis in children presenting to the Royal Liverpool Children's Hospital, Liverpool, UK and the Queen Elizabeth Central Hospital in Blantyre, Malawi: a world of difference. Ann Trop Paediatr. 2006;26(1):29–37.
26. Mwangi I, Berkley J, Lowe B, Peshu N, Marsh K, Newton CR. Acute bacterial meningitis in children admitted to a rural Kenyan hospital: increasing antibiotic resistance and outcome. Pediatr Infect Dis J. 2002;21(11):1042–8.
27. Akpede GO. Presentation and outcome of sporadic acute bacterial meningitis in children in the African meningitis belt: recent experience from northern Nigeria highlighting emergent factors in outcome. West Afr J Med. 1995;14(4):217–26.
28. Yogev R, Guzman-Cottrill J. Bacterial meningitis in children: critical review of current concepts. Drugs. 2005;65(8):1097–112.
29. Scheld WM, Koedel U, Nathan B, Pfister HW. Pathophysiology of bacterial meningitis: mechanism(s) of neuronal injury. J Infect Dis. 2002;186 Suppl 2:S225–33.
30. Williams AJ, Nadel S. Bacterial meningitis: current controversies in approaches to treatment. CNS Drugs. 2001;15(12):909–19.
31. Kaplan SL, Goddard J, Van Kleeck M, Catlin FI, Feigin RD. Ataxia and deafness in children due to bacterial meningitis. Pediatrics. 1981;68(1):8–13.
32. Stosic-Opincal T, Kacar K, Stosic S, Lavrnic S, Peric V, Gavrilov M. The use of magnetic resonance and MR angiography in the detection of cerebral infarction – a complication of pediatric bacterial meningitis. Vojnosanit Pregl. 2005;62(9):645–8.
33. Dodge PR, Swartz MN. Bacterial meningitis – a review of selected aspects. II. Special neurologic problems, postmeningitic complications and clinicopathological correlations. N Engl J Med. 1965;272:1003–10. CONCL.
34. Dodge PR, Swartz MN. Bacterial meningitis – a review of selected aspects. II. Special neurologic problems, postmeningitic complications and clinicopathological correlations. N Engl J Med. 1965;272:954–60. CONTD.
35. Ashwal S, Tomasi L, Schneider S, Perkin R, Thompson J. Bacterial meningitis in children: pathophysiology and treatment. Neurology. 1992;42(4):739–48.
36. Minns RA, Engleman HM, Stirling H. Cerebrospinal fluid pressure in pyogenic meningitis. Arch Dis Child. 1989;64(6):814–20.
37. Molyneux EM, Walsh AL, Forsyth H, Tembo M, Mwenechanya J, Kayira K, et al. Dexamethasone treatment in childhood bacterial meningitis in Malawi: a randomised controlled trial. Lancet. 2002;360(9328):211–8.
38. Snow RW, Guerra CA, Noor AM, Myint HY, Hay SI. The global distribution of clinical episodes of Plasmodium falciparum malaria. Nature. 2005;434(7030):214–7.
39. Okiro EA, Hay SI, Gikandi PW, Sharif SK, Noor AM, Peshu N, et al. The decline in paediatric malaria admissions on the coast of Kenya. Malar J. 2007;6:151.
40. Nyarango PM, Gebremeskel T, Mebrahtu G, Mufunda J, Abdulmumini U, Ogbamariam A, et al. A steep decline of malaria morbidity and mortality trends in Eritrea between 2000 and 2004: the effect of combination of control methods. Malar J. 2006;5:33.
41. Idro R, Jenkins NE, Newton CR. Pathogenesis, clinical features, and neurological outcome of cerebral malaria. Lancet Neurol. 2005;4(12):827–40.
42. Idro R, Marsh K, John CC, Newton CR. Cerebral malaria: mechanisms of brain injury and strategies for improved neurocognitive outcome. Pediatr Res. 2010;68(4):267–74.
43. Brown H, Rogerson S, Taylor T, Tembo M, Mwenechanya J, Molyneux M, et al. Blood-brain barrier function in cerebral malaria in Malawian children. Am J Trop Med Hyg. 2001;64(3–4):207–13.
44. Brown HC, Chau TT, Mai NT, Day NP, Sinh DX, White NJ, et al. Blood-brain barrier function in cerebral malaria and CNS infections in Vietnam. Neurology. 2000;55(1):104–11.
45. Waller D, Crawley J, Nosten F, Chapman D, Krishna S, Craddock C, et al. Intracranial pressure in childhood cerebral malaria. Trans R Soc Trop Med Hyg. 1991;85(3):362–4.

46. Newton CR, Crawley J, Sowumni A, Waruiru C, Mwangi I, English M, et al. Intracranial hypertension in Africans with cerebral malaria. Arch Dis Child. 1997;76(3):219–26.
47. Newton CR, Krishna S. Severe falciparum malaria in children: current understanding of pathophysiology and supportive treatment. Pharmacol Ther. 1998;79(1):1–53.
48. Looareesuwan S, Wilairatana P, Krishna S, Kendall B, Vannaphan S, Viravan C, et al. Magnetic resonance imaging of the brain in patients with cerebral malaria. Clin Infect Dis. 1995;21(2): 300–9.
49. Idro R, Karamagi C, Tumwine J. Immediate outcome and prognostic factors for cerebral malaria among children admitted to Mulago Hospital, Uganda. Ann Trop Paediatr. 2004;24(1):17–24.
50. Newton CR, Kirkham FJ, Winstanley PA, Pasvol G, Peshu N, Warrell DA, et al. Intracranial pressure in African children with cerebral malaria. Lancet. 1991;337(8741):573–6.
51. Newton CR, Hien TT, White N. Cerebral malaria. J Neurol Neurosurg Psychiatry. 2000; 69(4):433–41.
52. Carter JA, Ross AJ, Neville BG, Obiero E, Katana K, Mung'ala-Odera V, et al. Developmental impairments following severe falciparum malaria in children. Trop Med Int Health. 2005;10(1): 3–10.
53. John CC, Bangirana P, Byarugaba J, Opoka RO, Idro R, Jurek AM, et al. Cerebral malaria in children is associated with long-term cognitive impairment. Pediatrics. 2008;122(1):e92–9.
54. Mallewa M, Vallely P, Faragher B, Banda D, Klapper P, Mukaka M, et al. Viral CNS infections in children from a malaria-endemic area of Malawi: a prospective cohort study. Lancet Glob Health. 2013;1(3):e153–60.
55. Schubart CD, Mturi N, Beld MG, Wertheim PM, Newton CR. Role of viruses in Kenyan children presenting with acute encephalopathy in a malaria-endemic area. Am J Trop Med Hyg. 2006;75(6):1148–50.
56. Mallewa M, Fooks AR, Banda D, Chikungwa P, Mankhambo L, Molyneux E, et al. Rabies encephalitis in malaria-endemic area, Malawi, Africa. Emerg Infect Dis. 2007;13(1):136–9.
57. Lahat E, Barr J, Barkai G, Paret G, Brand N, Barzilai A. Long term neurological outcome of herpes encephalitis. Arch Dis Child. 1999;80(1):69–71.
58. Rautonen J, Koskiniemi M, Vaheri A. Prognostic factors in childhood acute encephalitis. Pediatr Infect Dis J. 1991;10(6):441–6.
59. Kolski H, Ford-Jones EL, Richardson S, Petric M, Nelson S, Jamieson F, et al. Etiology of acute childhood encephalitis at The Hospital for Sick Children, Toronto, 1994–1995. Clin Infect Dis. 1998;26(2):398–409.
60. UNAIDS. Together we will end AIDS. UNAIDS; 2012.
61. Bakaki P, Kayita J, Moura Machado JE, Coulter JB, Tindyebwa D, Ndugwa CM, et al. Epidemiologic and clinical features of HIV-infected and HIV-uninfected Ugandan children younger than 18 months. J Acquir Immune Defic Syndr. 2001;28(1):35–42.
62. Drotar D, Olness K, Wiznitzer M, Guay L, Marum L, Svilar G, et al. Neurodevelopmental outcomes of Ugandan infants with human immunodeficiency virus type 1 infection. Pediatrics. 1997;100(1):E5.
63. GM A, Assefa G. Clinical and neuroimaging profile of HIV-1 encephalopathy in infancy and childhood in a sub-Saharan African country. Ethiop Med J. 2012;50(4):337–47.
64. Giuliano Ide C, de Freitas SF, de Souza M, Caramelli B. Subclinic atherosclerosis and cardiovascular risk factors in HIV-infected children: PERI study. Coron Artery Dis. 2008;19(3):167–72.
65. Berger JR, Scott G, Albrecht J, Belman AL, Tornatore C, Major EO. Progressive multifocal leukoencephalopathy in HIV-1-infected children. AIDS. 1992;6(8):837–41.
66. Sacktor N, Nakasujja N, Skolasky R, Robertson K, Wong M, Musisi S, et al. Antiretroviral therapy improves cognitive impairment in HIV+ individuals in sub-Saharan Africa. Neurology. 2006;67(2):311–4.
67. Patel K, Ming X, Williams PL, Robertson KR, Oleske JM, Seage 3rd GR. Impact of HAART and CNS-penetrating antiretroviral regimens on HIV encephalopathy among perinatally infected children and adolescents. AIDS. 2009;23(14):1893–901.
68. Sacktor N, Nakasujja N, Robertson K, Clifford DB. HIV-associated cognitive impairment in sub-Saharan Africa – the potential effect of clade diversity. Nat Clin Pract Neurol. 2007;3(8): 436–43.

69. Melikian G, Mmiro F, Ndugwa C, Perry R, Jackson JB, Garrett E, et al. Relation of vitamin A and carotenoid status to growth failure and mortality among Ugandan infants with human immunodeficiency virus. Nutrition. 2001;17(7–8):567–72.
70. WHO. Global tuberculosis control 2009: surveillance, planning, financing; World Health Organization. 2009.
71. Donald PR, Schaaf HS, Schoeman JF. Tuberculous meningitis and miliary tuberculosis: the rich focus revisited. J Infect. 2005;50(3):193–5.
72. Leonard JM, Des Prez RM. Tuberculous meningitis. Infect Dis Clin North Am. 1990;4(4): 769–87.
73. Thwaites GE, Tran TH. Tuberculous meningitis: many questions, too few answers. Lancet Neurol. 2005;4(3):160–70.
74. Roos KL. Pearls and pitfalls in the diagnosis and management of central nervous system infectious diseases. Semin Neurol. 1998;18(2):185–96.
75. Holdiness MR. Management of tuberculosis meningitis. Drugs. 1990;39(2):224–33.
76. Winkler AS, Friedrich K, Konig R, Meindl M, Helbok R, Unterberger I, et al. The head nodding syndrome – clinical classification and possible causes. Epilepsia. 2008;49(12):2008–15.
77. Idro R, Opoka RO, Aanyu HT, Kakooza-Mwesige A, Piloya-Were T, Namusoke H, et al. Nodding syndrome in Ugandan children – clinical features, brain imaging and complications: a case series. BMJ. 2013;3(5):e002540.
78. Sejvar JJ, Kakooza AM, Foltz JL, Makumbi I, Atai-Omoruto AD, Malimbo M, et al. Clinical, neurological, and electrophysiological features of nodding syndrome in Kitgum, Uganda: an observational case series. Lancet Neurol. 2013;12(2):166–74.
79. Tumwine JK, Vandemaele K, Chungong S, Richer M, Anker M, Ayana Y, et al. Clinical and epidemiologic characteristics of nodding syndrome in Mundri County, southern Sudan. Afr Health Sci. 2012;12(3):242–8.
80. WHO. International scientific meeting on nodding syndrome. Geneva 2012.
81. Dowell SF, Sejvar JJ, Riek L, Vandemaele KA, Lamunu M, Kuesel AC, et al. Nodding syndrome. Emerg Infect Dis. 2013;19(9):1374–84.
82. Centers for Disease Control (CDC). Nodding syndrome – South Sudan, 2011. MMWR. 2012;61(3):52–4.
83. Foltz JL, Makumbi I, Sejvar JJ, Malimbo M, Ndyomugyenyi R, Atai-Omoruto AD, et al. An epidemiologic investigation of potential risk factors for nodding syndrome in Kitgum district, Uganda. PLoS One. 2013;8(6):e66419.
84. Idro R, Musubire KA, Byamah Mutamba B, Namusoke H, Muron J, Abbo C, et al. Proposed guidelines for the management of nodding syndrome. Afr Health Sci. 2013;13(2):219–32.
85. Makani J, Cox SE, Soka D, Komba AN, Oruo J, Mwamtemi H, et al. Mortality in sickle cell anemia in Africa: a prospective cohort study in Tanzania. PLoS One. 2011;6(2):e14699.
86. Diallo DA. Sickle cell disease in Africa: current situation and strategies for improving the quality and duration of survival. Bull Acad Natl Med. 2008;192(7):1361–72. Discussion 72–3.
87. Fleming AF. The presentation, management and prevention of crisis in sickle cell disease in Africa. Blood Rev. 1989;3(1):18–28.
88. Makani J. Stroke in sickle cell disease in Africa: case report. East Afr Med J. 2004;81(12): 657–9.
89. Makani J, Williams TN, Marsh K. Sickle cell disease in Africa: burden and research priorities. Ann Trop Med Parasitol. 2007;101(1):3–14.

Part IV
Testing and Investigating Brain Degeneration in Sub-Saharan Africa: The Case of Uganda

Chapter 14
Review of Reasons for Patients to Receive a CT of the Head and Neck Region in Uganda in 2011–2012

Stanley Jacobson, Tammy Hsieh, Nathan Yuen, Samuel S. Giles, and Rosemary Kusaba Byanyima

Abstract This paper describes the reasons for 403 patients to receive a CT-scan of their head and neck in the Department of Radiology of the Mulago Hospital in Kampala Uganda in 2011–2012. The objective of this study was to determine the indications for this imaging investigation and the total percentage of patients with each indication. The study undertook to answer these three major questions: 1) Which were the most common indications for a CT-Brain scan? 2) Was there a gender difference in the imaged patients? 3) Were there age differences in each category of the imaged patients?

We examined 403 cases and noted these 16 different indications for Brain CT scans:

Head Trauma, Cerebral Vascular Accident (CVA), Space Occupying Lesion (SOL), Head Symptoms, Brain Tumors, Cryptococcus/Toxoplasmosis/HIV Meningitis, Headache, Seizures, Spinal Symptoms, Facial Injury, Dementia, Congenital Anomalies, Follow up, Psychiatric indications, Encephalitis and Loss of Consciousness (LOC). For each category we included the number of cases with the gender and age of the patient being imaged.

Head trauma and especially from Road Traffic Accidents (RTA) was the most common indication for a Brain CT-scan request forming 48 % of the cases.

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S. Musisi, S. Jacobson (eds.), *Brain Degeneration and Dementia in Sub-Saharan Africa*, DOI 10.1007/978-1-4939-2456-1_14

The many Road Traffic Accidents, 48% of the cases, were due to the presence of small motor bike taxis called “boda-boda”. CVA were the second most common indications forming 11 %. Combined, RTA and general trauma to the head form a major burden on the country.

In terms of gender, for the 403 cases we reviewed 277 (69 %) were males while 126 (31 %) females. In all categories of trauma generally, more males than females were affected and this was especially more so in RTA cases where 119 males and only 35 females were imaged. In the cases of assault, more males (32) than females (4) were affected, and finally in cases of trauma due to a fall again more males (9) than females (4) were affected. The few elderly patients (those above 60) that were seen with dementia were primarily females. As for age, in each category, there were more young males (age-bracket 14–44 years) than females. Still this was more evident in the cases of Trauma and CVA.

Keywords CT-scan images • Cerebro-vascular accidents (CVA) • Dementia • Gender • Road traffic accidents (RTA) • Trauma • Traumatic brain injury

Abbreviations

Boda-boda	Small ubiquitous motor cycle taxis
CHI	Closed head injuries
y.o.	Years old
CT-scan	Computer tomography scan
CVA	Cerebrovascular accidents
HIV/AIDS	Human immunodeficiency virus/acquired immunodeficiency syndrome
NCD	Non-Communicable Disease
OHI	Open head injuries
RTA	Road Traffic Accidents
SOL	Space Occupying Lesions
TBI	Traumatic Brain Injury

Introduction

This paper describes the reasons for patients receiving a CT-scan image of their head-neck region in 2011 and 2012 in the Department of Radiology of the Mulago Hospital Complex in Kampala, Uganda. Mulago Hospital in Kampala is the major national referral hospital in the country. It has a bed capacity of over 1,700 but at times the numbers of inpatients are more than the available beds hence creating floor cases. The government allocation to the health sector is on average 9.6 % of the total government budget (GOU 2010) with the hospital consuming approximately 12 % [5] of the national health budget.

The objectives of this study were to determine:

1. Which were the most common indications for a head and neck CT-scan at Mulago Hospital?
2. Was there a gender difference in the imaged patients?
3. Were there age differences in each category of the imaged patients?

Materials and Methods

Collection of Cases

Every year there are over 7,200 CT-scan studies of the Head-Neck region made in the Department of Radiology of Mulago Hospital. The majority of these cases are due to trauma from road traffic accidents, RTA.The vast majority of these records are currently in the form of paper charts or files. With the aid of the staff in the Department of Radiology, charts were collected from 2011–2012 for 403 patients. These charts were selected at random and were then scanned digitized, and analyzed they formed the basis of this study.

Prior to imaging all the patients were given a physical examination including a neurological examination. When there were abnormalities present they had a CT-scan and then an analysis of their images with a clinical diagnosis. The diagnosis listed for each patient was performed by the radiologists of the Department of Radiology in Mulago Hospital.

CT-Scan Analysis

All the patients in this study had a CT image only after abnormalities were found on their physical or neurological examination. All the CT images were obtained on a MX 16 Philips CT Scanner acquired in August 2010.

Image Reconstruction

The DICOM images that were collected by the Philips CT Scanner were reconstructed to demonstrate 3D features were analyzed on a 4 channel Mac Pro running Leopard 10.5 and 3D reconstructions were made using OsiriX 5.0.

Results

For this study we reviewed the digitized file charts from 403 patients and we found the indications to be 16 different categories which are discussed below and are listed in Table 14.1 and Fig. 14.1. The 16 different categories were arranged in frequency of imaging as follows: Head Trauma, Cerebral Vascular Accidents (CVA), Space Occupying Lesion (SOL), Head Symptoms, Tumors, Spinal Symptoms,

Table 14.1 List of reasons (indications) for patients to undergo CT-brain scans at Mulago Hospital, Kampala

Reason	Total #	Subclass	#
Trauma	**195**	**RTA: Boda-Boda 135, Auto 19.**	**154**
		Normal	14
		Assault	**28**
		Fall	**13**
CVA	**46**	**Ischemic**	15
		Hemorrhagic:	28
		(Subdural	10
		Epidural	2
		Intracranial	13
		Interventricular)	3
		Normal	3
Exclude SOL (space occupying lesion)	**33**		
Head symptoms	**24**	**Ear**	5
		Mouth	1
		Nasal	3
		Optic	14
		Skull	1
Tumor	**19**	**Neural**	5
		Non-neural	14
Seizure	**12**		
Toxoplasmosis/HIV	**12**		
Headache	**12**		
Spinal symptoms	**10**		
Facial injury	**10**	**Trauma**	5
		Palsy	4
		Tumor	1
Dementia	**8**		
Congenital abnormalities	**7**		
Follow up	**5**		
Psychiatric disorders	**4**		
Encephalitis	**3**		
LOC (loss of consciousness)	**3**		
Grand total	**403**		

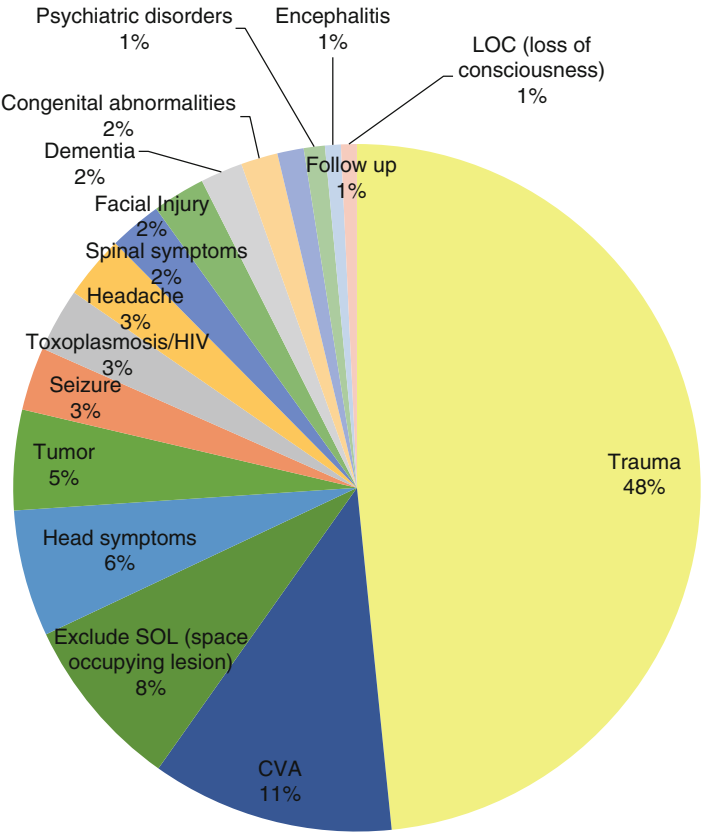
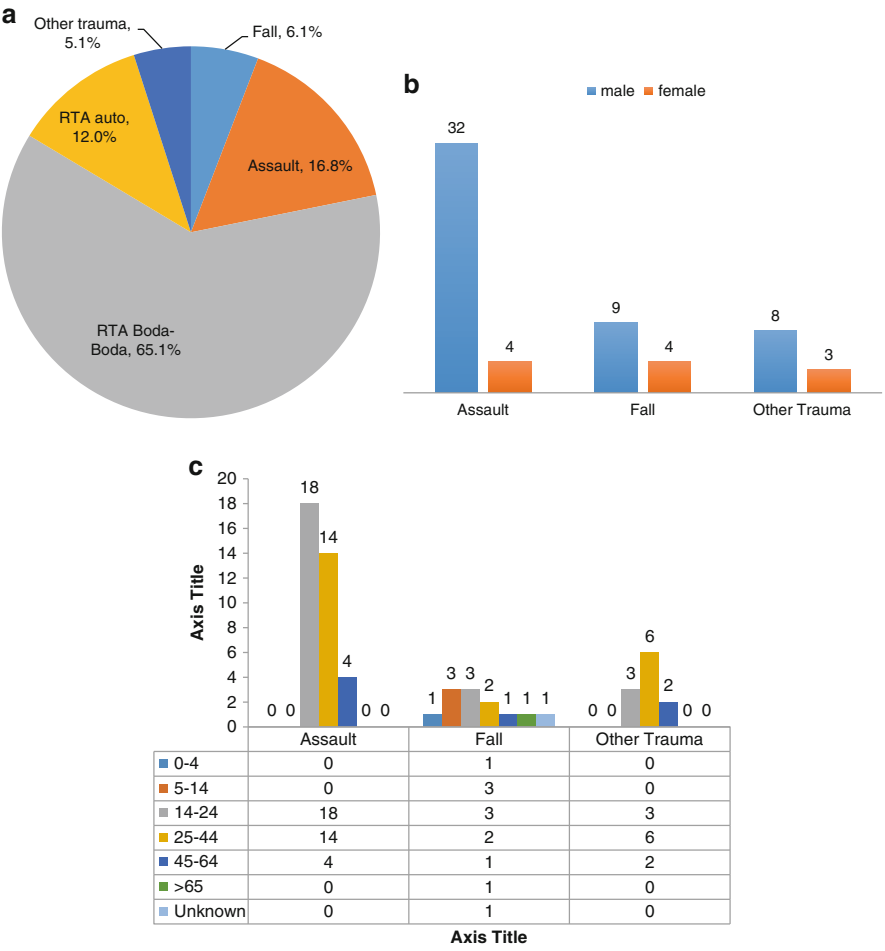


Fig. 14.1 Pie Chart demonstrating

Cryptococcus/Toxoplasmosis/HIV meningitis, Headache, Seizures, Facial Injury, Dementia, Congenital Anomalies, Follow up, Psychiatric indications, Encephalitis and Loss of Consciousness (LOC). In each category we also included the number of cases with the gender and age of the patient being imaged.

What Where the Most Common Indications That Required a Head-Neck CT-scan? (Fig. 14.2)

We found the majority of the indications were due to Trauma which involved 48 % of the cases followed by Cerebrovascular accidents, CVAs, as the next most common indications affecting 11 % of the cases.



	Assault	Fall	Other Trauma
0-4	0	1	0
5-14	0	3	0
14-24	18	3	3
25-44	14	2	6
45-64	4	1	2
>65	0	1	0
Unknown	0	1	0

Fig. 14.2 (**a**) Trauma subclasses; (**b**) gender distribution of trauma subclasses; (**c**) age distribution of trauma subclasses

Head Trauma (Fig. 14.2)

We identified a total of 197 patients that were imaged due to a traumatic incident and in this category abnormalities were noted in CT-scans from 154 cases of road traffic accidents, RTAs, 28 cases of Assault and 15 cases due to a fall.

Road Traffic Accidents or RTAs, (Fig. 14.2a), formed 77 % of the total cases of head trauma. There were 154 cases of trauma due to RTA with 10 % (14 cases), demonstrating no abnormalities in their CT head scans. The vehicles that were

involved in these accidents were in 12 % (19 of the cases) due to accidents in automobiles or trucks while the majority, 88 % (135 patients) were due to accidents on the small ubiquitous motor bike taxis called "boda-boda" in Uganda (Table 14.1).

Traumatic Brain Injuries (TBI)

Of the 154 patients with trauma from RTA, 89 % had traumatic brain injuries, TBI, while 61 % of the imaged patients due to assaults and falls had TBI. In the RTA sub-category, males were more commonly affected with 119 males vs. 34 females (Fig. 14.3a) and the most common ages of the affected were in the 14–44 year age bracket (Fig. 14.3b).

In Fig. 14.3c in the RTA category we noted that the patients that were imaged due to head injuries consisted of 47.2 % with closed head injuries (CHI), and 37.7 % with open head injuries. All the patients that had either open or closed head injuries had neurological deficits. Of the patients admitted for evaluation of head injuries, 14 % were found to have no abnormalities in their head CT-scan images.

Trauma Due to Either Assault or a Fall (Fig. 14.2a–c)

The other common causes of trauma which led to a patient being imaged included 28 cases of Assaults and this formed 13 % of the cases of trauma, and 13 (6 %) were cases of Falls with 10 % of these cases showing no abnormality in their CT-scan images. These assault and fall injuries were more common in males in 49 cases vs. 11 in females There were another 10 cases listed with 5 of them having brain edema from many sources including infections. The remaining 5 cases were from other forms of unspecified causes and these were all without any abnormalities in their CT-scan images.

Imagery of Skull Fractures from RTA

Figure 14.3d–h, are examples of skull fractures seen in several of the patients caused by RTAs.

Figure 14.3d, CT-brain scan of RTA: Fracture of Frontal Bone in male age 24 with headaches following RTA.

Figure 14.3e. Case of RTA. 3D reconstruction of fracture of frontal bone shown in Fig. 14.3d of a male age 24. OsiriX Open Source imaging Software version 5.9.

Figure 14.3f. Case of RTA. 3D reconstruction of a fracture of left Occipital bone in male age 14 with headaches following RTA. OsiriX Open Source imaging Software version 5.9.

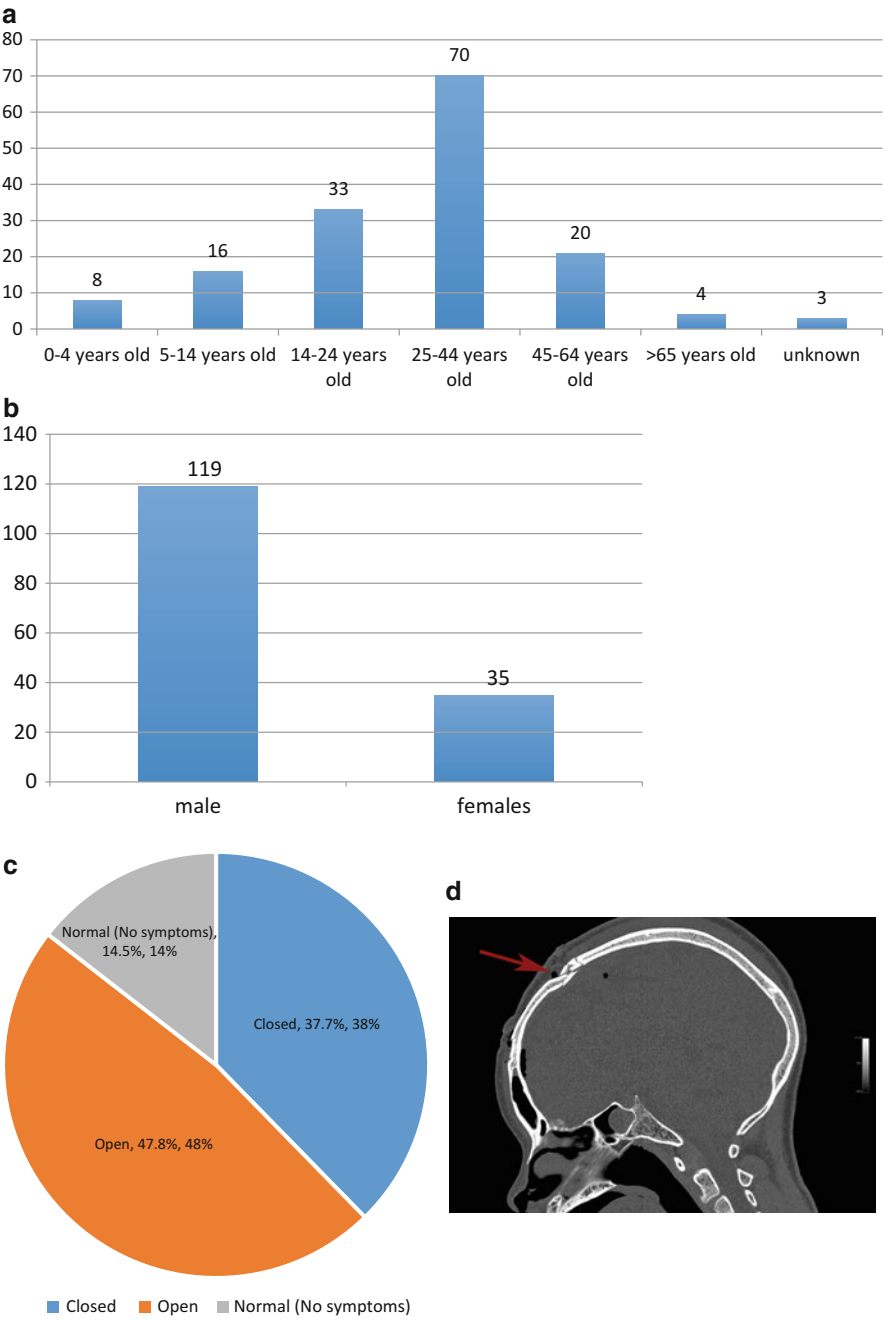


Fig. 14.3 (**a**) RTA head injury age demographic by age; (**b**) RTA head injury gender demographic; (**c**) RTA head injuries open head injuries vs. closed head injuries; (**d**) CT, sagittal image, fracture of frontal bone, *red arrows*, after RTA, male age 24 with headaches, *red arrow*; (**e**) 3D reconstruction of skull shown in (**d**) with fracture of frontal bone, *red arrows*, in a male age 24 (OsiriX imaging Software version 5.9); (**f**) RTA 3D reconstruction of a skull with a fracture, *red arrow*, of left occipital bone in male age 14 with headaches (OsiriX imaging Software version 5.9);

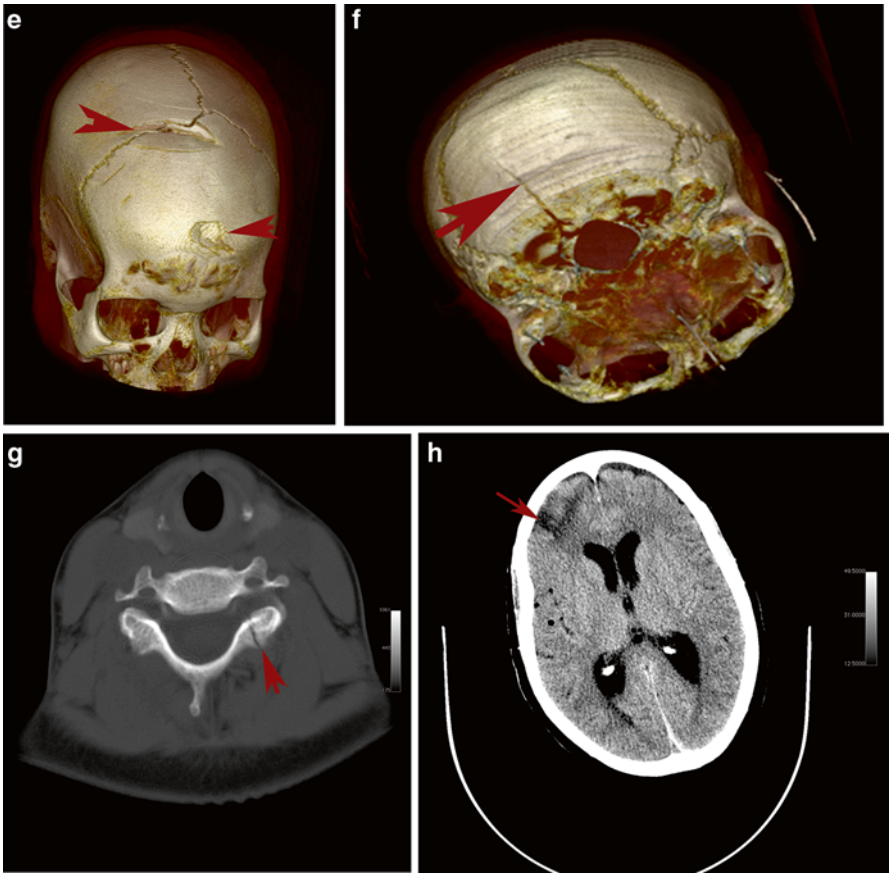


Fig. 14.3 (continued) (**g**) RTA CT fracture of left lamina, *red arrow*, in cervical vertebrae C2 male age 19 with pain and some muscular symptoms; (**h**) RTA. CT image demonstrating the effects of an intracerebral contusion to the right frontal polar cortex due to a RTA in a 64 year old female. The patient demonstrated some changes in personality and upper motor neuron signs on the left side of the body

Cerebrovascular Accidents (CVA)

Table 14.1 lists cerebrovascular accidents, CVA, as the second most common indication for imaging after trauma forming 46 (11 %) of the total imaged cases. In the CVA category 43 cases (93 %) had significant cerebral lesions upon examination of their CT-scan images as a consequence of the CVA. Only 6.5 % of these cases had no abnormalities in their CT images or in their neurological examination.

The types of CVA as noted in Fig. 14.4a were 68 % hemorrhagic and 32 % ischemic.

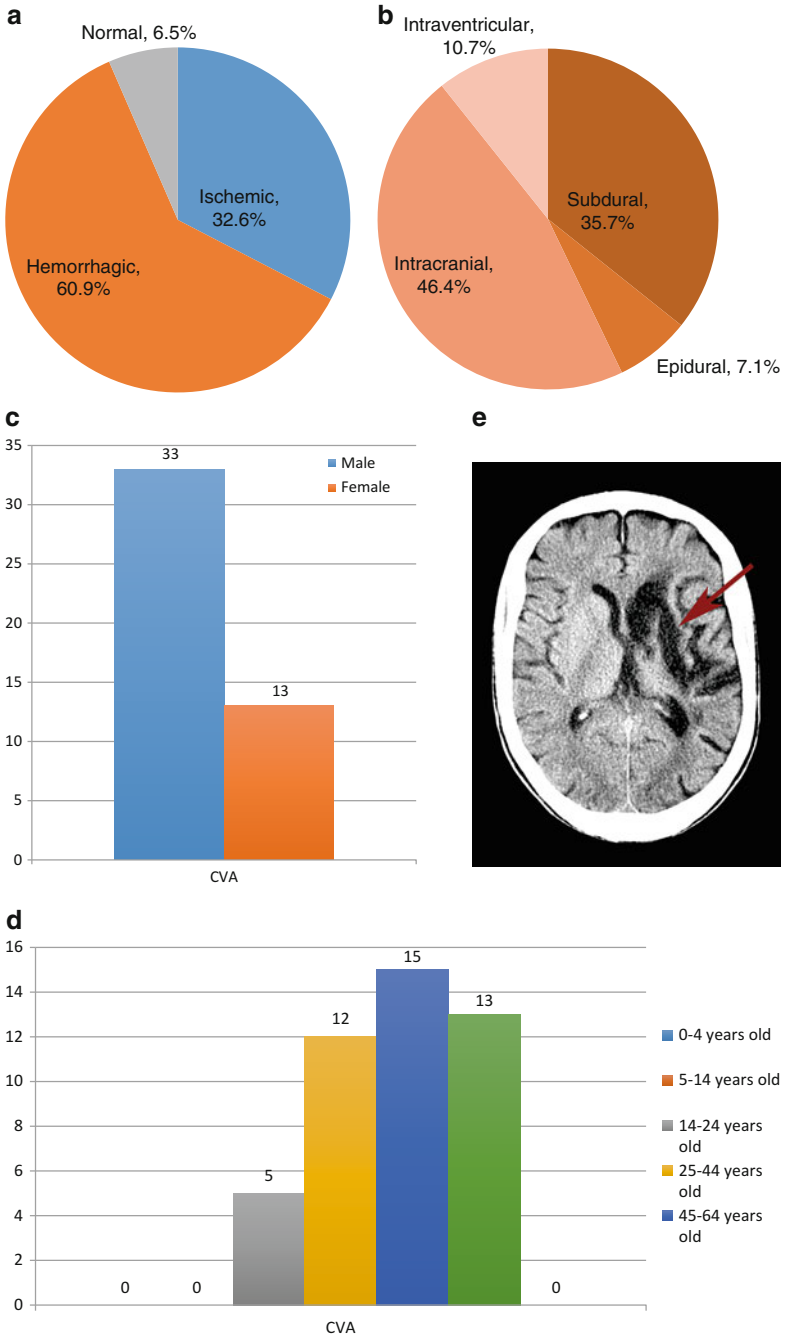


Fig. 14.4 (**a**) CVA. The types of CVA were 68 % hemorrhagic and 32 % ischemic; (**b**) CVA. The locations of the 28 cases with hemorrhagic lesions were divided as follows: epidural 2/7 %, subdural 10/35 %, intraventricular 3/10.7 %, and intracranial 13/46.4 %; (**c**) Gender of patients with CVA. They were more common in males with 33 while 13 females affected; (**d**) Age of patients with CVA. The ages affected were primarily from 14–64 y.o; (**e**) This is a CT from a 60 year old male patient with a CVA in the distribution of the inferior branch of the left MCA with an infarct into the left Inferior Frontal Gyrus and Insular cortex, *red arrow*, with Broca's motor aphasia and upper motor neuron symptoms in the right arm

The locations of the 28 cases with hemorrhagic lesions as shown in Fig. 14.4b were divided as follows: epidural 2 (7 %), subdural 10 (35 %), intraventricular 3 (10.7 %), and intracranial 13 (46.4 %). The cases with ischemic lesions were located throughout the brain.

The CVAs were more common in males with 33 with 13 being females (Fig. 14.4c).

The most commonly affected ages, as noted in Fig. 14.4d, were from 14 to 64 y.o.

Figure 14.4e is a CT-head scan from a 60 year old male patient with a CVA in the distribution of the inferior branch of the left MCA with an infarct into the left Inferior Frontal Gyrus and insular cortex with Broca's motor aphasia and upper motor neuron symptoms in the right arm.

Space Occupying Lesions (SOL): Table 14.1 and Fig. 14.1

There were 33 cases (8 %) of the total imaged cases that were due to suspected space occupying lesions. In this category there were 17 females and 16 males, a 1:1 ratio in the affected.

Head Symptoms: Table 14.1 and Fig. 14.1

There were 24 cases, with 5 cases (6 %) of the total having involvement of the ear; 5 cases mouth; 3 cases nose; 3 cases, eyes; 14 cases skull, One of Six of the cases associated with the eye had some neurological signs including double vision and pupillary signs while the other cases were within normal limits. In this category there were 14 males and 10 females affected.

Brain Tumors (Table 14.1 and Fig. 14.1)

There were 19 cases with brain tumors forming, 5 % of the total cases. In this group there were 5 intracranial cases and, 14 with non-intracranial involvement. The 5 cases with intracranial tumors exhibited abnormal neurological signs. In this category there were 10 males and 9 females affected.

Seizures, Cryptococcus/Toxoplasmosis/HIV, and Headache

In this category there were 12 cases being 3 % of the total, as shown in Table 14.1 and Fig. 14.1. The seizures were either a consequence of a RTA, CVA or HIV. The Cryptococcus/Toxoplasmosis/HIV cases were noted in patients who were either

not responding to the antiretroviral treatment or not taking their medicines regularly. There was an equal number of males and females affected with 6 of each gender.

Spinal Symptoms

In the category of spinal symptoms, there were 10 cases, being 2 % (Table 14.1 and Fig. 14.1). The spinal symptoms were associated with RTA (Fig. 14.3g). There were more cases of spinal cord injuries in males than females: 7 cases to 3.

Facial Injuries

Facial injuries were noted in 10 cases being 2 % of the total (Table 14.1 and Fig. 14.1). There were 5 facial injuries due to trauma and 4 palsies with two of these cases being of Bell's palsy, and 1 due to a facial tumor. Facial injuries were more common in males than females 6 to 4.

Dementia

A referral for dementia was noted in 8 cases or 2 % of the total cases (Table 14.1 and Fig. 14.1) with 7 females and 1 male. The cases of dementia were in elderly patents being over 60 with 7 being females and one male. in the general population in Uganda the elderly are reported to be 4–6 % [5].

Congenital Anomalies

Congenital anomalies formed 7 cases, being 2 %, (Table 14.1 and Fig. 14.1). One case included a Siamese twin. There were 4 males and 3 females.

Follow Ups

Patients that were referred back for follow up CT images formed 1 %, with all 5 cases being due to RTA (Table 14.1 and Fig. 14.1). In the follow ups there were 3 males and 2 females.

Psychiatric Disorders

Referrals from Psychiatric illnesses formed 4 cases, 1 % of the total (Table 14.1 and Fig. 14.1). There were 2 males and females that were imaged.

Encephalitis

Encephalitis was noted in 3 cases all related to malaria, 1 % (Table 14.1 and Fig. 14.1).

Loss of Consciousness

Loss of Consciousness, LOC, formed 3 cases, 1 % of total. They were related in two cases to Trauma and one case to a CVA (Table 14.1 and Fig. 14.1).

Were There Gender Differences in Each Category?

In the 403 cases we reviewed 277 were in males and only 126 in females giving a Male:Female ratio of 9:5 or 1.8:1. In all categories of trauma, more males were affected. In RTA cases more males were affected than females; 119 and 35, respectively (Fig. 14.3b). In assault cases, also more males were affected than females; 32 and 4 respectively (Fig. 14.2c). Finally in cases of trauma due to a fall, again more males than females were affected; 9 vs. 4 respectively (Fig. 14.2c). In the other cases of trauma, these were also more common in males than females; 8 vs. 3 respectively (Fig. 14.5b).

In CVAs (Table 14.1 and Fig. 14.4c), of the 46 cases 33 (71 %) were in males and 13 (29 %) were in females. There were also 3 cases (2 males and 1 female) that were imaged for a CVA but the images were within normal limits.

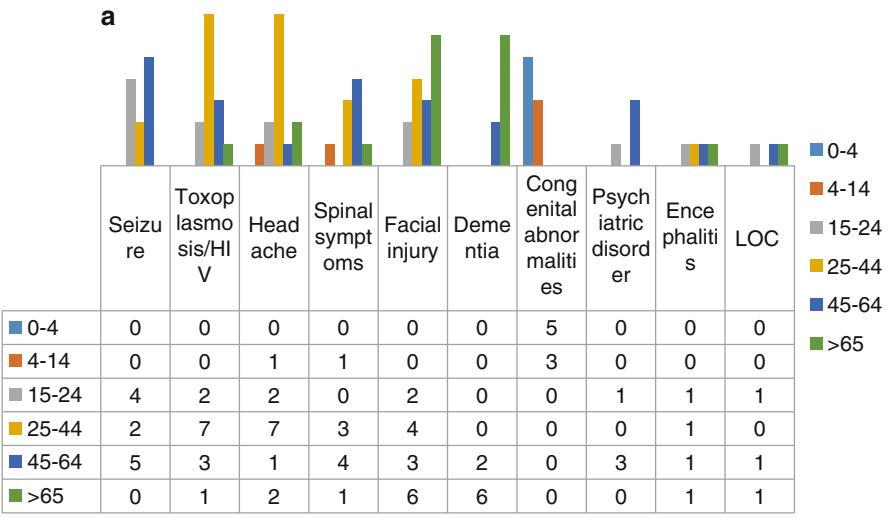
Congenital abnormalities were noted in 5 females and 2 males (Fig. 14.4c).

Dementia was noted in only 8 cases (Fig. 14.5b). In the patients who were screened for dementia there were 7 females and 1 male.

Were There Age Differences in Patients in Each Category? (Figs. 14.3a, d, and 14.5a)

Trauma In all categories more younger males were affected as evidenced in the RTA, assaults and falls (Fig. 14.3a) from ages 14–44 y.o.

a



	Seizure	Toxoplasmosis/HIV	Headache	Spinal symptoms	Facial injury	Dementia	Congenital abnormalities	Psychiatric disorder	Encephalitis	LOC
0-4	0	0	0	0	0	0	5	0	0	0
4-14	0	0	1	1	0	0	3	0	0	0
15-24	4	2	2	0	2	0	0	1	1	1
25-44	2	7	7	3	4	0	0	0	1	0
45-64	5	3	1	4	3	2	0	3	1	1
>65	0	1	2	1	6	6	0	0	1	1

b

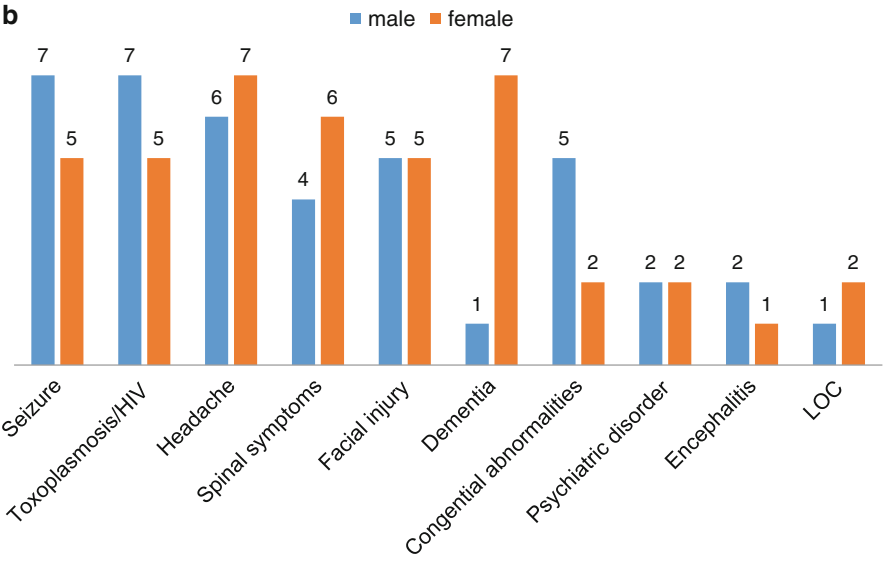


Fig. 14.5 (**a**) Age distribution of other maladies imaged; (**b**) gender distribution of other maladies imaged

In CVAs (Fig. 14.4d), the age range was 14–64+ and more males were affected with the majority being from age 25–64+.

Dementia Cases formed only 8 cases, 1 male and 7 females. The patients ranged in age from 60 and older (Fig. 14.5a).

Discussion

Non-Communicative Diseases

In another paper in this book [4] we noted the similarity seen in the percent of neurodegenerative, non-communicative diseases of the brain seen in Africa and in the United States and Europe due to our common origin out of Africa many thousand years ago [9]. However, since occurrence of these migrations millenia ago, many environmental factors have since influenced the non-communicable disease process in the central nervous system and especially the resultant extension in the life cycles in the higher income regions of the world. In these higher income regions there are many positive improvements in public health, but also a major increase in the presence of many cases of neurodegenerative disease and especially Alzheimer's' disease as the population ages. In Uganda which is a lower income region, the vast majority of the 403 records that were reviewed were of patients of less than 50 years of age.

Dementia, in our study only constituted 8 of 403 (2 %) patients that were imaged. They were all over 60 years in age with 7 of the 8 (87.5 %) being female. In a study in Tanzania, Mavrodaris, Powell and Thorogood [8] noted that there was a major problem in accurate data collecting in the sub-Saharan African region as there were only a few electronic data bases. When more data base will be formed one should have a more accurate and complete insight on the amount of age-related dementia in the region. Paddick et al. [10] observed that dementia and other non-communicative diseases will become an increasing burden on health services in Sub-Saharan Africa as the NCD population ages due to the control of the communicative disease of malaria, HIV/AIDS and TB [7].

Communicable Diseases

Currently malaria is the leading cause of illness (morbidity and mortality) in all communicable diseases in these regions (CDC and WHO 2013). In our 403 cases there were only 12 patients imaged for malaria and for HIV AIDS. Even though there are still too many cases of malaria and HIV/AIDS in Uganda most of these cases are diagnosed without CT-scan imagery. UNICEF has shown encouraging results in the reduction in the number of children, with cases of malaria, HIV/AIDS and malnutrition. However, there are still too many people that are affected by these diseases (WHO 2012).

Trauma

In regard to Trauma, in this review of the patients undergoing a CT-head scans, 195 of the 403 (48 %) of the patients were imaged due to trauma (Table 14.1 and Fig. 14.1) males aged 14–44 years were most commonly affected (Figs. 14.2c, 14.3b, 14.4c,

and 14.5b). For the RTA, a major difference is noted in the vehicles involved in the countries with higher income than in countries with lower incomes. In the higher income regions the accidents are primarily in automobiles while in lower income countries including Uganda the accidents are primarily with the smaller motor cycles called "boda-boda" which offer the riders very little protection [15]. These small motor bikes are widely used throughout East Africa and in many of the lower income countries such as India and Bangladesh [6, 11]). The results of our study confirm the burden placed on Uganda by the many cases of trauma, the vast majority of which are due to accidents on these small motor bikes, the "boda-bodas".

Traumatic Brain Injury (TBI)

In our study TBI was caused by RTA, falls, and accidents. The data from the WHO [15] and the World Bank [13], shows that RTAs are the leading cause of TBI in the world [15]. TBI are the leading cause of death and disability in children and young adults in the world and they cause about half of the deaths that result from trauma [16].

The data from the World Health Organization and the World Bank [13] also notes that RTA injuries cause considerable economic losses to the victims, their families, and to nations as a whole. These losses arise from the cost of treatment (including rehabilitation) as well as lost productivity (e.g. in wages) for those killed or disabled by their injuries, and for family members who need to take time off work (or school) to care for the injured.

About 1.2 million people die worldwide each year as a result of road traffic accidents [15] with road traffic injuries the leading cause of death among young people, aged 15–29 years and more males than females are affected.

Road Traffic Accidents (RTA) cause 91 % of the world's traffic fatalities and these mostly occur on the roads of low-income and middle-income countries, even though these countries have approximately only half of the world's vehicles [13]. Only 28 countries in the world, from the higher income regions of the world representing 416 million people and they contain less than 10 % of the world's current population. These high income countries have laws that address all five of the risk factors involved in RTA – speed, drink-driving, helmets, seat-belts and child restraints [3]. Uganda with a rate of 28.9 deaths per million due to the numerous RTA is in the top percentile of the world's deaths caused by RTAs [12] (WHO and World Bank 2014). As we noted in our study RTA formed the bulk of the patients imaged. Over 90 % of these cases had TBI, (Fig. 14.2b). One shouldn't be surprised that the CT facilities are nearly overwhelmed by these accidents.

*Cerebro-Vascular Accidents (*CVAs*)*

Table 14.1 and Fig. 14.1 lists CVAs as the next most common cause for CT brain imaging after trauma forming 46 or 11 % of the total cases. Only 3 or 7 % of the CVA cases had no abnormalities in their CT-scan images or on their neurological

examination. In the other 43 cases with CVAs, in 93 %, there was TBI in their CT-scan images. The lesions as noted in Fig. 14.4a were 67 % hemorrhagic and 33 % ischemic. The 28 cases with hemorrhagic lesions, (Fig. 14.4b), were divided as follows: epidural 2(7 %), subdural 10(35 %), interventricular 3(10.7 %), and intracranial 13(46.4 %). The CVAs were more common in males, 33 cases vs. only 15 females cases affected, (Fig. 14.4c).The need for prevention of stroke and especially the control of hypertension has been noted in Sub-Saharan Africa by Chin [2] and Addo, Smeeth and Leon [1], and there have been improvements noted [14].

Much progress has been made in the treatment of malnutrition and in malaria prevention by adding mosquito netting as well as in the prevention of HIV/AIDS [14]. However NCD such as hypertension and the RTA with its deleterious consequences have not yet been addressed in most lower income countries. In our review of the 403 patients undergoing a CT head scans, 197 trauma cases were imaged (Fig. 14.2a) and 154 of the trauma cases were due to Road Traffic Accidents with 89 % of the RTA cases demonstrating TBI. In the total number of 154 RTAs, 135 or 88 % were due to accidents on the small motor bikes (boda-boda) with only 12 % as result of automobile or truck accidents (Table 14.1).

How Does One Counteract the Many Deleterious Effects of the RTA Due to the Ubiquitous Small Motor Bikes the Boda-Bodas?

The reality is that in Kampala, motor bikes or boda-boda taxis, since their introduction in the 1990s, do provide jobs and plug the gaping holes in the public transport system. They have become ubiquitous and indispensable with frequent accidents which often are deadly [6, 11]. In Kampala there are fleets of these two-wheeled motor cycles and no one knows exactly how many there are, but the local media reports that there may be as many as 300,000 boda-bodas on the streets of the Ugandan capital, always on the lookout for passengers [6, 11]. The City of Kampala has recently begun to address this problem by expanding its public transport with the acquisition of buses, and there have been progress in better training the drivers of these motorcycles. However driving and riding boda-bodas is an easy means to get around the city and also provides many jobs in a country with high unemployment [6]. One method that is being championed and could lead to a great reduction in frequency and the consequences of RTA is The Global Helmet Vaccine Initiative [3]. This Initiative which has not yet caught on, offers much promise for the future as it is trying to train drivers how to drive safely, and also convince them and their patrons to purchase and to wear helmets. This is an effort to stop the occurrence of so many TBI without banning bikes altogether.

References

1. Addo J, Smeeth L, Leon DA. Hypertension in Sub-Saharan Africa: a systematic review. Hypertension. 2007;50:1012–8.
2. Chin JC. Stroke in Sub-Saharan Africa: an urgent call for prevention. Neurology. 2012; 78(13):1007–8.
3. Seat-belts and child restraints: a road safety manual for decision-makers and practitioners London, FIA Foundation for the Automobile and Society, 2009
4. Giles S, Jacobson S, and Byanyima R. Anatomy of normal and degenerative. In:Brain Degeneration and Dementia in Sub-Saharan Africa, S. Musisi and S. Jacobson Eds, Springer Publication 2015.
5. The Government of Uganda GOU. Printing Office, Kampala Uganda. 2013.
6. Lagarde E. Road traffic injury is an escalating burden in Africa and deserves proportionate research efforts. PLoS Med. 2007;4:170–176.
7. Longdon A, Kisoli A, Unwin N, Alberti KG. Chronic non-communicable diseases. Ann Trop Med Parasitol. 2006;100:455–64.
8. Mavrodaris A, Powell J, Thorogood M. Prevalence of dementia and cognitive impairment among older people in sub-Saharan Africa: a systematic review. Bull WHO. 2013;91:773–83.
9. Moreno E. The society of our "out of Africa" ancestors. The migrant warriors that colonized the world. Commun Integr Biol. 2013;6(3):e24145. Published on line.
10. Paddick SM, Longdon AR, Kisoli A, Dotchin C, Gray W, Dewhurst F, Chaote P, Kalane R, Jusabani A, Walker R. Demential prevalence estimates in sub-Saharan Africa: comparison of two diagnostic criteria. Glob Health Action. 2013;6:19646.
11. Chalya PL, Mabula JB, Dass RM, Mbelenge N, Gilyoma MJ. Injury characteristics and outcome of road traffic crash victims at Bugando Medical Centre in Northwestern, 2006.Tanzania. J Trauma Manag Outcomes. 2012;6:1. Published online Feb 9, 2012.
12. United Nations International Children's Emergency Fund. The state of the World's Children. UNICEF Publication 2014.
13. World Bank. Transport for health: the global burden of disease from motorized road transport. Global road safety facility, the world bank; institute for health metrics and evaluation (2014-03-31) world bank open knowledge depository. 2013.
14. World Health Organization. Publication. United Nations high-level meeting on non-communicable disease prevention and control NCD summit to shape the international agenda. 2011.
15. World Health Organization Publication. The top 10 causes of death. 2014.
16. World Health Organization Publication. Neurological disorders: public health challenges. 1. Nervous system diseases. 2. Public health. 3. Cost of illness. 2006.

Chapter 15
CT Findings in the Brain of Adult Patients with HIV/AIDS

Rosemary Kusaba Byanyima

Abstract The availability of modern imaging techniques of Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) scans have enabled us to investigate and study brain conditions of HIV CNS involvement commonly seen in Sub-Saharan Africa. Computed Tomography scan of the head displays a two dimensional anatomy of the brain in the form of cross-sectional images enabling one to see structures enclosed within the skull bones. The structural changes due to intracranial pathologies can be easily detected and administration of intravenous iodinated contrast medium further characterizes these lesions to aid in diagnosis. The earlier radiological methods of investigating intracranial pathology, like pneumoencephalography, conventional angiography or even skull x-rays were invasive or provided limited information. Ultrasound is only applicable in young children before closure of the fontanelle or if adults in the presence of a bone defect, like a burr hole.

This chapter will review degenerative brain changes in HIV/AIDS patients due to HIV-related infections, viremia, malignancy, neuronal death, demyelination or those involving the meninges, ventricles, arachnoid matter and also lesions due to bleeds from a variety of causes. However, normal Contrasted CTs were also a common finding despite documented HIV CNS involvement. This calls for more stringent guidelines for ordering this, expensive but otherwise new and modern useful neuro-imaging investigation.

Keywords Neuroimaging • CT • MRI • Encephalitides • Demyelination • HIV/AIDS • Opportunistic infections • Brain edema • Headache • Central Nervous System (CNS) • Dementia • Meningitis

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S. Musisi, S. Jacobson (eds.), *Brain Degeneration and Dementia in Sub-Saharan Africa*, DOI 10.1007/978-1-4939-2456-1_15

Abbreviations

HIV	Human immunodeficiency virus
CSF	Cerebrospinal fluid
SPECT	Single photon emission computed tomography
CM	Cryptococcal meningitis
PML	Progressive multifocal leukoencephalopathy
CMV	Cytomegalovirus
CNS	Central nervous system
PET	Positron emission tomography
MRI	Magnetic resonance imaging
CT	Computed tomography
CCT	Cranial computed tomography

Introduction

The availability of cross sectional imaging techniques like Computed Tomography and Magnetic Resonance Imaging machines; Single-Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) Scans has revolutionized neuro-imaging [1]. Computed Tomography scan of the head displays two dimensional anatomy of the brain in form of cross-sectional images enabling one to see structures enclosed within the skull bones. The structural changes due to intracranial pathologies can be easily detected and administration of intravenous iodinated contrast medium further characterizes these lesions to aid in diagnosis.

The earlier Radiological methods of investigating intracranial pathology, like pneumo-encephalography and conventional angiography are invasive and yet provide limited information. Plain skull x-rays and linear tomography are rarely informative. Ultrasound is only applicable before closure of the fontanelle or in presence of a bone defect, like a burr hole.

In this study we will review the records of 151 patients referred for CT scan examination at the Mulago National Referral Hospital. Our goal is to determine the number of patients and their gender in Uganda in the year 1997 with intracranial pathology due to the HIV infection and also to note the associated pathological and neurological symptoms.

Materials and Methods

Neuro-Radiology and Imaging

Radiological methods of investigating intracranial infections include conventional Radiography, Angiography, Radionuclide imaging, Ultrasound, CT and MRI of the cranium [2–5]. Magnetic Resonance Imaging, Single Photon Emission Computed

Tomography (SPECT) and Positron Emission Tomography (PET) are the more advanced imaging modalities [6, 7]. These are more sensitive because they also assess functional status in addition to structural anomalies of the brain.

A Philips Tomoscan CX/Q 1994 model was used. Pre- and post-contrast axial scans were performed for all patients. Clinical and laboratory results were collected. Final diagnosis was based on laboratory results, surgical findings, response to treatment and/or post-mortem findings.

CT Imaging Technique, Cross-Sectional Descriptive Study in the Mulago Hospital Radiology Department

Patients with CNS symptoms who were also HIV positive, and had the WHO AIDS clinical diagnostic criteria were included in this study. A standard cranial CT consists of a series of contiguous tomographic sections of 5 mm or less, thickness. This is performed with the patient laying supine on examination couch. Patients are scanned initially without intravenous iodinated contrast medium and then post-intravenous contrast administration [1]. For adult patients of average size a dose of about 40 ml of 76 % iodinated low osmolar contrast medium given by free hand injection into a peripheral superficial vein is sufficient. The laboratory results from Mulago Hospital are also included.

Pathological Findings

Viral encephalitis is confirmed from histopathology specimens from appearances of focal areas of white matter inflammation, demyelination and vacuolization's [2].

Illustrative Patients

We have included CT images and case histories for illustrative HIV patients with brain abscess, toxoplasmosis, lymphoma, encephalopathy with cortical atrophy and intracranial hemorrhage.

Results

CSF Findings (Fig. 15.1)

In 91 of 105 patients in this study had a CSF analysis, and in this group 34 out of 91 had abnormal CSF including 3 with pyogenic organisms seen at Gram stain, 11 had capsulated yeast cells and 1 had AAFB (atypical acid fast bacteria). In 54 % of these cases there were abnormal CSF results without meningeal enhancement at CT.

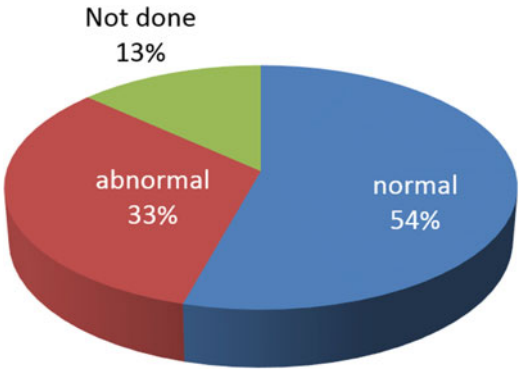

Fig. 15.1 CSF findings

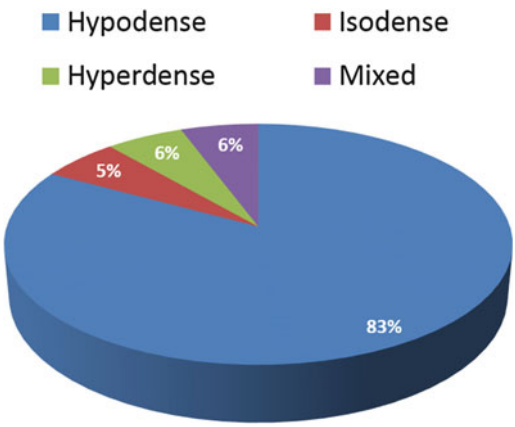

Fig. 15.2 Density of brain lesions

Density of Brain Lesions (Fig. 15.2 and Table 15.1)

Behavior with IV Contrast. In each case multiple lesions were a common feature and 50.5 % had detectable brain lesions. In these cases 83.0 % of lesions were hypo dense, with 39.6 % in white matter, 26. 4 % in the Basal ganglia. In the analysis of CT findings after iv contrast, Table 15.1, 47.2 % were non-enhancing, 30.2 % were ring shaped and 20.8 % were nodular in appearance. Patients with lymphomas usually had single lesions while patients with toxoplasmosis had multiple lesions.

Table 15.1 Behavior of IV contrast

Pattern	Number	Percentage
Non enhancing	25	47.2
Ring	16	30.2
Nodular	11	20.8
Not applicable	1	1.9
Total	**53**	**100.0**

Table 15.2 Clinical features

Clinical features	No. abnormal	% abnormal
Headache	61	76.3
Vomiting	16	55.2
Convulsions	19	48.7
Photophobia	7	53.8
Fever	56	78.9
Neck rigidity	23	82.1
Kernig's sign	20	90.9
Altered consciousness	18	56.3
Focal neurological signs	43	64.2

Clinical Signs and Symptoms of HIV Infected Patients

Fever and headache are the most frequent symptoms in these HIV patients (Table 15.2). The clinical features listed in Table 15.2 may not be a specific symptom of CNS diseases with headache due to irritation of the meninges and arteries with their associated pain nerve fibers. The headache as a symptom is subjective, sometimes ambiguous and its severity difficult to assess. The fifth, ninth and tenth cranial nerves contain pain fibres are also found in the meninges and are recording the meningeal irritation and sending it into the brain. Headache may therefore be due to cranial neuralgias, meningeal irritation, vascular disturbances and traction of intracranial structures which have pain nerve fibers. Neck rigidity and positive Kerning's sign are absent in 58.8 % of patients with abnormal cranial CT results. This may reflect subacute meningitides from *Cryptococcal* and TB infections which rarely give signs of meningeal irritation [2].

The brain parenchyma, pia-arachnoid, ventricular linings and choroid plexuses are insensitive [8].

Neurological Signs

Focal neurological signs (Table 15.3) were encountered in 63.8 % of the patients in this study and these are usually strong predictors of presence of structural lesions at CT (P value = 0.0004). It has been observed from other populations of AIDS patients

Table 15.3 Focal CNS signs

Signs	Number	Percentage
Focal CNS signs	67	63.8
Altered consciousness	32	30.5
Neck rigidity	28	26.7
Kerning's sign	22	21.0

that the frequency of CNS symptoms is about 30 % and at postmortem the occurrence of CNS abnormalities is as high as 80 % [2]. By the time of death many of these patients demonstrate more pathological lesions that were not detected by CT imaging.

Altered consciousness is the second common predictor of presence of structural lesions (P value = 0.568) and Kerning's sign the least. These neurological manifestations result from opportunistic infections or from primary involvement of the brain by the HIV and primary CNS lymphomas [9, 10]. Although CNS infections, including syphilis, bacterial meningitis, brain abscesses, and tuberculosis are seen in HIV infected individuals, cryptococcal meningitis and toxoplasmosis predominates [11–14]. Most patients present with severe persistent headache, fever and lethargy. Peculiar to toxoplasmosis is focal neurological abnormalities, confusion and seizures in addition to the general symptoms mentioned above (see Fig. 15.10).

Final Clinical Diagnosis

Final clinical diagnosis and clinical correlation in this study are listed in Fig. 15.3, with Toxoplasmosis 28 % of the cases, *cryptoccal* meningitis 18 %, and bacterial meningitis 8 %. Tuberculous meningitis and viral encephalitis each form 4 % of the cases. Depression and cerebral malaria were each 3 % and PML, Hemorrhagic strokes, bacterial cerebritis, pyrogenic empyema, subacute subdural were 1–2 % of the cases,

Abnormal CT Appearances

In the current study 63 % of the patient's had focal CNS findings. The frequency of brain structural lesions in another study one study in Uganda in 1998 was 50.5 %. The available literature gives a lower percentage of between 20 and 40 % [15–17]. This high frequency of mass lesions in this study is probably related to the patients who were referred for CT examination were very ill thus with more obvious lesions including a higher rate of complicating opportunistic infection. Lesions also exhibit variable contrast enhancement depending on vascularization and brake down of the blood–brain barrier.

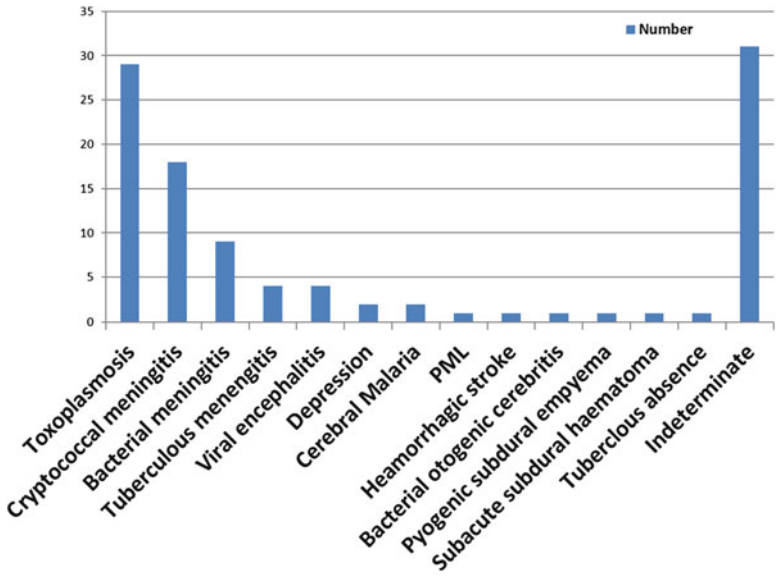

Fig. 15.3 Final diagnosis

Appearance of Intracranial Infections

Opportunistic lesions (Fig. 15.4) of the CNS occur are caused directly by HIV infection and there can be other complications including dementia, cerebral toxoplasmosis, Cryptococcal meningitis (CM) and progressive multifocal leukoencephalopathy (PML).

Diffuse white matter hypodense non-enhancing lesions are seen in PML, CMV and HIV encephalitis.

Toxoplasmosis causes chronic necrotizing inflammation of the brain that appears as necrotic foci in which tachyzoites and/or cysts can be seen. At the edge of these foci, inflammatory infiltrates and multinucleated giant cells are found [2]. Calcifications often ensue later as well as atrophy and later small gliotic scars form.

The CT appearances of intracranial infections are characteristic [2, 18–20]. In this study the majority of lesions are hypo dense on CT without contrast administration as they are inflammatory. They appear hypo dense due to the edema which is of low attenuation (see Fig. 15.1 and Table 15.1).

Brain abscesses have a characteristic "doughnut" appearance. The pre-contrast scan shows a hypodense lesion (Fig. 15.4). The hypodense area in the center represents non-viable debris, while the ring enhancing and the peripheral hypodense area represent the capsule and edema respectively. The increased tissue water content in inflammatory lesions gives low attenuation co-efficiencies in comparison with normal brain. The normal brain grey and white matter Hounsfield readings are in the range of 36–46 and 22–32 respectively [20].

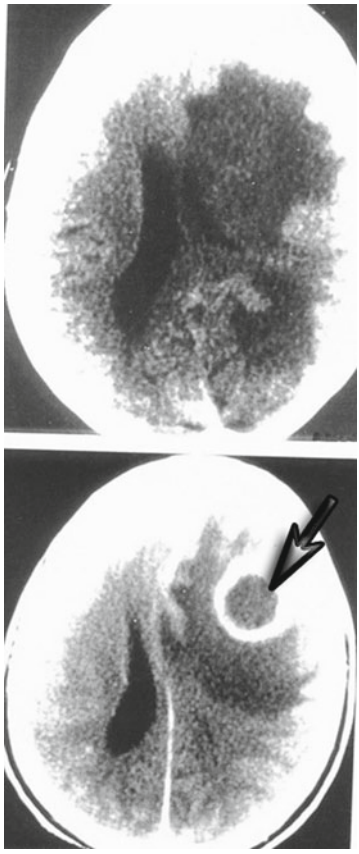

Fig. 15.4 A 29 year old female presented with right sided body weakness, fever and reduced level of consciousness. Enhanced CT scan results show a ring enhancing lesion in left frontal lobe with gross surrounding edema. The patient improved on antibiotic therapy and surgical drainage which confirmed a pyogenic abscess

Figure 15.4 demonstrates ring and nodular lesions. The lesion shows ring enhancement post-contrast with marked surrounding edema. This was confirmed as a pyogenic abscess following surgical drainage.

Figure 15.5 illustrates the pathological features of meningitis at postmortem examination.

Encephalitis (Figs. 15.6, 15.7, 15.8, and 15.9) is associated with little or no change in CT appearance of the brain. Ill-defined hypo dense areas without focal enhancement may be the only finding. Non-enhancing lesions are also highly prevalent accounting for 47.2 % is cases of CNS lesions. Intracerebral lesions do enhance with I.V. contrast medium if they are highly vascular or if there is breakdown of the blood brain barrier. There are patients with non-enhancing lesions who had toxoplasmosis. This is explained by the fact that failure of capsule formation around toxoplasmosis abscesses in extreme immune-suppression, 5 % of these lesions do not enhance. Lack of enhancement in cerebral toxoplasmosis encephalitis is a poor prognostic sign [21]. Hypodense periventricular white matter lesions without con-

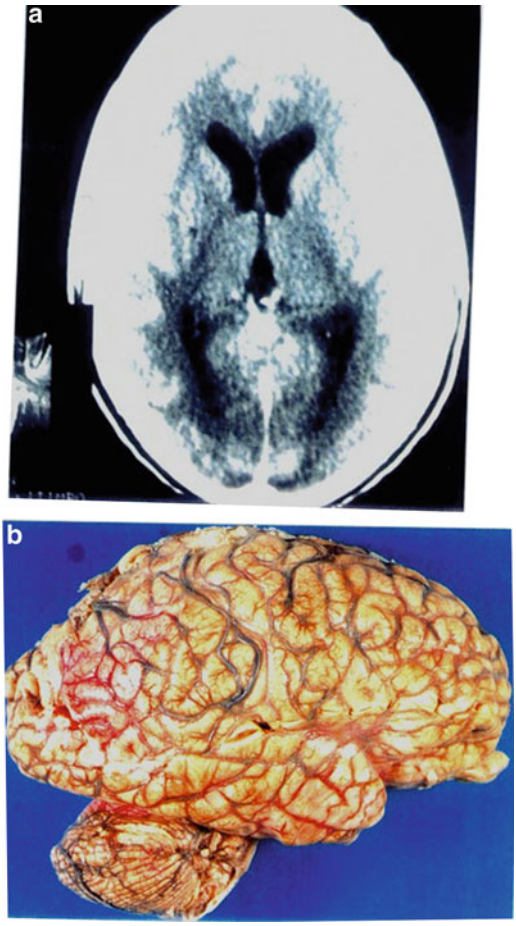

Fig. 15.5 A 31 y.o. male presented with history of fever, severe headache and left 6th cranial nerve palsy. Enhanced CT scans (**a**) show marked generalized meningeal enhancement. Patient passed away, and postmortem gross specimen (**b**) revealed mucoid whitish appearance over the brain most marked in the Sylvain fissures and post-central sulcus

trast enhancement are diagnostic of encephalitis. When these CT signs are clinically associated with rapidly progressing dementia, PML (progressive multifocal leukoencephalopathy) is the likely cause [22]. In one patient with PML we confirmed the diagnosis at postmortem with histological.

HIV encephalitis gives fairly symmetrical white matter hypodense lesions which have no mass effect and do not enhance. Histologically in PML the abnormalities are due to the JC papovirus damaging the oligodendrocytes resulting in edema and demyelination. Necrosis may ensue ultimately [2]. MRI is more sensitive at diagnosing these white matter lesions [23, 24].

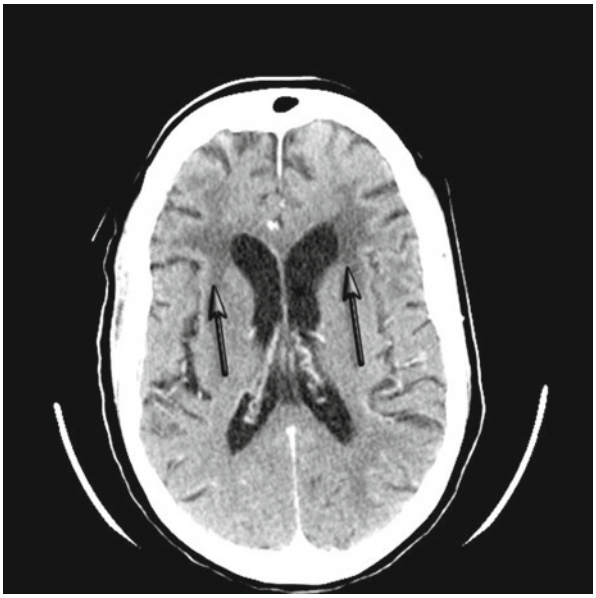

Fig. 15.6 Female 58 y.o. HIV encephalitis with diabetes mellitus. Encephalitis is evident in presence of hypodense lesions in the white matter (*arrows*) of the frontal and parietal lobe. Patient had convulsions associated with mental confusion. CD-4 355, toxin negative

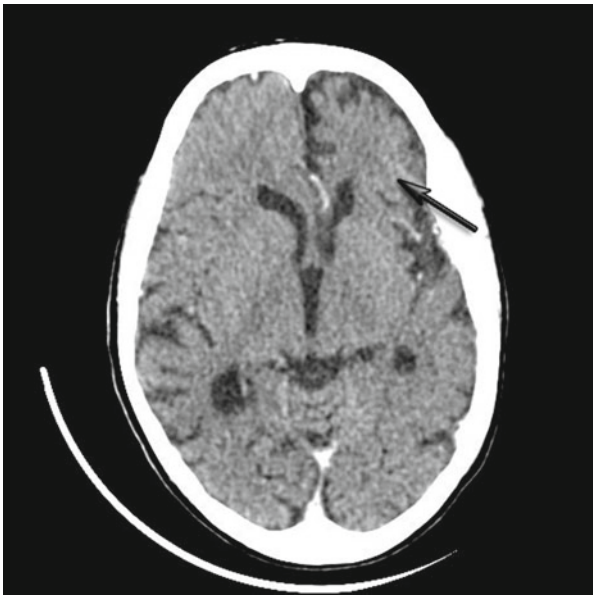

Fig. 15.7 Male 8 y.o. with HIV encephalopathy with epilepsy and marked atrophy in left cerebral hemisphere (*arrow*)

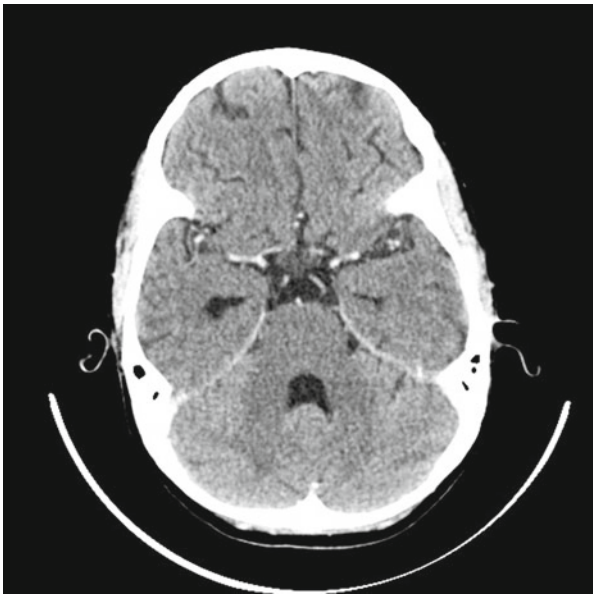

Fig. 15.8 Female 13 y.o. with HIV Encephalitis with brain swelling on ART holiday due to poor adherence and severe bone marrow suppression. On TB treatment also has very low CD4-2 cells. Clinical presentation with dizziness, and vomiting

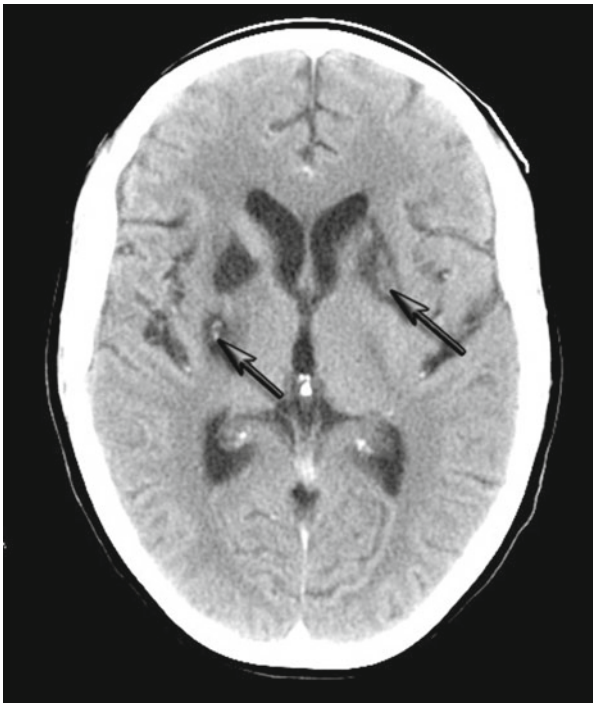

Fig. 15.9 A 58 y.o. female with bilateral infarcts in internal capsule (*arrows*) and left-sided hemiplegia. No response to high-dose septrin

Cases 3, 4, 5 and 6 (Figs. 15.6, 15.7, 15.8, and 15.9) demonstrate the diverse effects of encephalitis on the brain including atrophy, and hypo density in the white matter and also resultant neuronal degeneration within the brain.

The neurological findings in Case 6 (Fig. 15.9) acutely in this patient were similar to those of a stroke but in this HIV positive patient one should also remember that lymphomas cause chronic necrotising inflammation of the brain that appears as necrotic foci in which tachyzoites and/or cysts can be seen which were seen here.

Lymphoma

Primary intracranial Lymphoma which behaves like Toxoplasmosis on contrasted CCT scans is the second commonest cause of brain mass lesions [25]. Lymphoma, Metastatic Kaposi's sarcoma and thrombocytopenia may lead to intracerebral haemorrhage [26, 27]. It should however be remembered that in the immune suppressed, primary intracerebral lymphoma tends to be peripherally located and this may help differentiate it from Toxoplasmosis. Focal contrast enhancing lesions may be due to Crytococcoses can be diagnosed more readily with laboratory backup. Granulomas associated with these two are usually cortical in location with accompanying features of meningitis. Toxoplasmosis and Lymphomas have similar CT features. They usually appear as multiple enhancing mass lesions in the basal ganglia and white matter [7].

Case 7 (Fig. 15.10) is an example of the effects of a lymphoma on the brain.

Other causes of white matter lesions which are difficult to confirm purely from CT features are HIV encephalitis, PML and other viral encephalitides [2, 18].

Notable abnormalities in meningitis include obliteration of the basal cisterns and contrast enhancements of the leptomeninges, however a normal brain CT scan may be found in early meningitis.

Empyemas appear as hypodense or isodense, crescentic extra-cerebral fluid collections. There is usually accompanying adjacent meningeal enhancement with or without cerebritis of the underlying cortex.

Cerebral Atrophy

Cortical atrophy is a common non-specific finding. It is commonly associated with infection of the CNS by HIV or other viruses. Widened sulcal spaces with accompanying ventriculo-megally are also frequent finding in HIV infected as a sign of brain volume loss commonly referred to as atrophy. In a study by Levy RM and co-workers, 200 patients with AIDS were reviewed and CCT revealed that 40 % of these patients with neurological symptoms had brain atrophy [28]. Case 8 (Fig. 15.11) is an example of cortical atrophy with widening of the sulci throughout the brain and seen in HIV positive patients.

Cerebral edema from inflammatory processes also masks the atrophy. Brain atrophy in AIDS patients is thought to be due to viral encephalitides and cerebral toxoplasmosis.

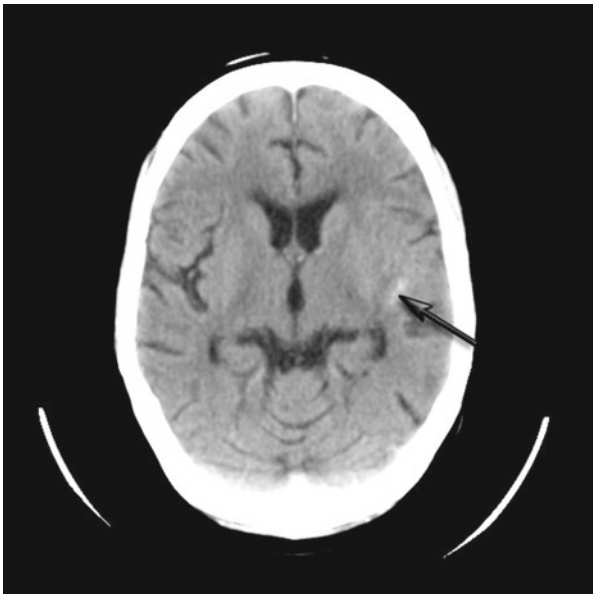

Fig. 15.10 Female 38 y.o. lymphoma with cortical atrophy, seropositive on TB treatment and ARV with convulsions and not speaking. Blood sugar normal but no LP done due to increased intracranial pressure

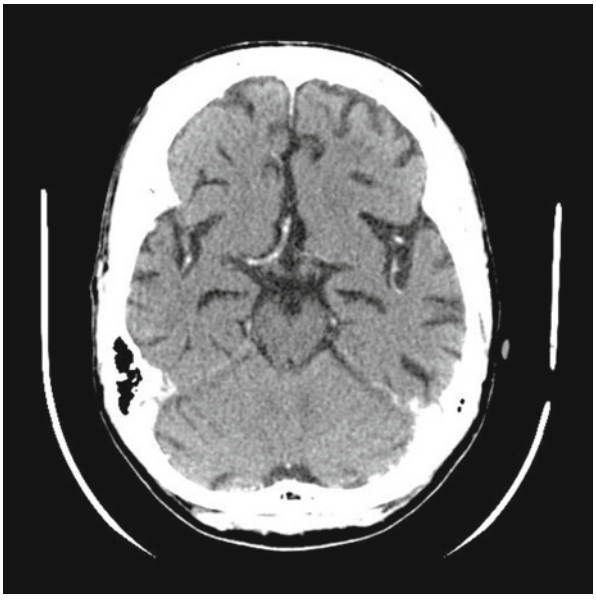

Fig. 15.11 Male 40 y.o. HIV positive with cortical atrophy, mental confusion associated with on and off headache

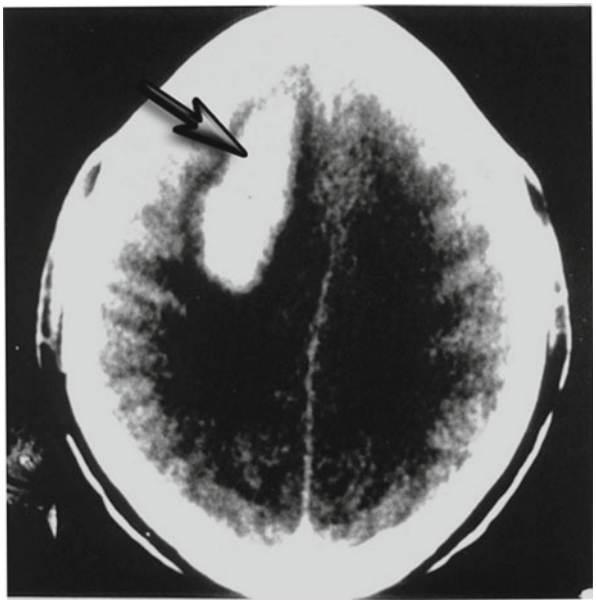

Fig. 15.12 Acute intracerebral hematoma. A 28 year old HIV positive female presented with history of menorrhagia and later developed left sided hemiparesis. Non-contrasted scans show hyper dense white matter frontal lobe lesion suggestive of acute intra-cerebral hematoma

Severe atrophy is not indicative of dementia. Other causes of dementia like Alzheimer's disease, neuro-syphilis, should be investigated for and excluded.

The commonest radiological diagnosis is normal CCT scan, followed by meningitis. Posterior fossa lesions can be obscured by beam hardening artifacts even when thin slices are used thus giving false negative results. MRI is the imaging modality of choice for this area.

Intracranial Hemorrhage

Brain infarcts are a rare finding (1.3 %). Predisposing factors include non-bacterial thrombotic endocarditis, Herpes arteritis. In Case 9 (Fig. 15.12) an HIV patient with an intracerebral hematoma this patient was not hypertensive and did not have a history of trauma had CT features of acute intra-cerebral hemorrhage. The patient had thrombocytopenia. It was later confirmed in this patient that low platelet count was the predisposing factor.

The mechanism by which HIV mediates thrombocytopenia is uncertain but the concurrent effects of medications and opportunistic infections may be considered. It has been postulated that production of auto-antibodies, hormonal inhibitory factors, T-cell mediated suppression of hemopoiesis and inhibitory cytokines may be contributory to the thrombocytopenia [29, 30].

Discussion

It has been noted that neurological complications occur in 40–80 % of patients with HIV infection [1], while in study 48 % of patients with intracranial pathology seen at CT were HIV infected. In our study 75.2 % of the HIV infected with associated CNS symptoms have abnormalities detectable at CT. At times neurological diseases may be the first clinical evidence of HIV infection.

Opportunistic Infections Associated with HIV

The most frequently identified HIV/AIDS related central nervous system diagnoses such as cryptococcal meningitis, Toxoplasmosis, HIV dementia, encephalitis, primary central nervous system lymphoma and progressive multifocal leucoencephalopathy have characteristics clinical and CT features. We also noted these lesions in our study.

Primary central nervous system Lymphomas in the AIDS patients as noted by others has almost similar appearance to Toxoplasmosis at CT [2]. Brain abscesses have a characteristic "doughnut" appearance on enhanced CT scans. The hypo dense center is non-viable debris; the ring enhancement represents the abscess capsule and the peripheral hypodense area, surrounding edema. Toxoplasmosis abscesses tend to be located in the basal ganglia and white matter.

Most encephalitides are associated with little or no change in CT appearance of the brain. Low attenuation areas without focal enhancement may be the finding. In early stages of meningitis, CT examination may be normal. Obliteration or narrowing of the basal cisterns and enhancement of the leptomeninges are the notable abnormalities in meningitis.

Empyemas appear as a hypodense or isodense crescentic, extra-axial collection. Empyemas are associated with adjacent meningeal enhancement and cerebritis of the underlying cortex although this is not a constant feature [1, 18–20].

Lymphomatous meningitis appears as diffuse meningeal enhancement at CT and the malignant cells are detectable in CSF. Metastatic Kaposi's sarcoma to the brain although very rare, will appear as ring enhancing lesions with surrounding edema [2].

Epidemiology of HIV in Sub-Saharan Africa: Uganda's Perspective

HIV-I infection was first recognized in Uganda in 1982. By the end of 1995, approximately 1.5 million Ugandans were infected with HIV largely through heterosexual transmission [31]. The HIV sero-prevalence was also measured and risk behavior assessed in three longitudinal cohorts of Ugandan regular military assembled between

1992 and 1995. The results from this study demonstrated that Uganda Military recruits had a high but stable HIV sero-prevalence rate [32, 33].

From 1990 to 1992 a study on the crude prevalence of HIV in a rural community with a mature epidemic was done, although this may have been a misleading indicator of the course of the epidemic [34]. Following this many studies were carried out in Uganda about the incidence, prevalence and risk factors for HIV infection in different communities [31–36].

Cases of TB and Cancer

Cases of tuberculosis infection increased dramatically and a corresponding increase in extra-pulmonary TB among the HIV infected individual was noted. The sero-prevalence for HIV among patients with TB was 40–47 % [37]. Tuberculosis may present as meningitis, meningo-encephalitis or as tuberculous abscesses. Tuberculomas may be single or multiple, of varying sizes, with variable degree of contrast uptake. Tuberculomas are usually located in the grey matter. Basal exudates which obliterate the basal cisterns are a common finding as well as beading of the arteries that form the circle of Willis [1, 18–20].

Likewise, the trend of cancers in Kampala-Uganda changed in the AIDS area [38]. This was thought be due to reduce immunity making the victims vulnerable to viruses associated with cancer, in addition to other factors [38, 39]. To date, there is apparent relationship between HIV and Lymphomas documented, but most striking feature has been emergency of Kaposi's Sarcoma as the leading cancer in males and second most frequent cancer in females [38, 39].

Indeterminate group pose dilemma, and there is a need for more advanced imaging techniques, laboratory tests and histopathology diagnosis. Pyogenic meningitis is still common in the HIV infected. CT scan examination was normal for 2 patients with cerebral malaria. The cause of subacute subdural hematoma and empyema was uncertain.

Clinical Presentation Gender Data

There is equal gender distribution of HIV infected patients with CNS symptoms in the Uganda case studies, which could be due to heterosexual transmission of HIV as compared to homosexual and intravenous drugs use in the western world [40]. The bimodal peak of male who are HIV infected and with CNS symptoms for age distribution (30–35 years and 40–45 years) and a single age peak for females (30–35 years) could be due to the practice of cross generational sex.

Conclusion

In this study 48 % of patients with intracranial pathology seen at CT were HIV infected. In this group 75.2 % of the HIV infected with associated CNS symptoms have abnormalities detectable at CT. Focal neurological signs are related to the presence of brain lesions at CT scan. Radiological appearances of these lesions are similar to those described in literature. Cerebro-vascular diseases are common in HIV infected patients but cerebral tumors are rare in HIV infected.

References

1. Grainger RG, Allison DJ. Diagnostic radiology, vol. 3. 3rd ed. London/New York: Churchill Livingstone Edinburgh; 1997. p. 2039–125.
2. Reeders JWAJ. Diagnostic imaging of AIDS. Stuttgart/New York: Georg Thieme Verlag Thieme Medical Publishers; 1992. p. 5–50.
3. Smith PR. Neuroradiology of intracranial infections. Pediatr Neurosurg. 1992;18(2):92–104.
4. Whelan MA, Kricheff I, Handler M. Acquired immuno deficiency syndrome: cerebral computed tomography manifestations. Radiology. 1983;149(2):477–84.
5. Grainger RG, Allison DJ. Diagnostic radiology, vol. 3. 3rd ed. London/New York: Churchill Livingstone Edinburgh; 1997. p. 2039–125.
6. Rosci MA, Pigorini F, Berbabei A, et al. Methods for detecting early signs of AIDS dementia complex in n asymptomatic HIV-in infected subjects. AIDS. 1992;6:1309–16.
7. Arendt G. Imaging methods as a diagnostic tool in neuro-AIDS. A review. Bildgebung. 1995;62(4):310–9.
8. Wyngaarden JB, Smith LH. Cecil textbook of medicine, vol. 2. 17th ed. Philadelphia/Tokyo: W.B. Saunders Company; 1976. p. 2054–60.
9. Lucas SB, Odida M, Wabinga H. The pathology of severe morbidity and mortality caused by HIV infection in Africa. AIDS. 1991;5:143–8.
10. Lucas S, Sewankambo N, Nambuya A, et al. The morbid anatomy of African AIDS. Basal: Karger; 1988. p. 123–33.
11. Oishi K, Mugerwa R, Mitarai S, et al. High mortality in AIDS patients with cryptococcal meningitis despite fluconazole therapy in Uganda. Int Conf AIDS. 1994;10(2):24 (Abstract no. 387B).
12. Baingana G, Katabira E, Hellman N. Neurologic disease in Uganda AIDS patients. Int Conf Aids. 1991;7(1):187 (Abstract No. M.B. 2021).
13. Baingana G, LeBlond RF, Sande M, et al. Clinical and laboratory features of cryptococcal meningitis in AIDS patients, Kampala, Uganda. Int Conf AIDS. 1992;8(2):B110 (Abstract No. PoB3139).
14. Baingana G, Grant R, Baingana B, et al. Predictors of survival among Ugandan AIDS patients with cryptococcal meningitis. Int Conf AIDS. 1993;9(1):368 (Abstracts no. PO-BO9-1399).
15. Kaisser G, et al. Neuor imaging of AIDS. Indiana Med. 1991;84(7):470–4.
16. Tso EL, Todd WC, et al. Cranial computed tomography in the emergency department evaluation of HIV – infected patients with neurologic complainants. Ann Emerg Med. 1993;22(7):1169–76.
17. Elkin CM, Leon E, Crenell SL, Leeds NE. Intracranial lesion in the acquired immune deficiency syndrome: radiological (computed tomography) features. JAMA. 1985;253(3):393–6.
18. Weisberg N. Cerebral computed tomography. A text-atlas. 3rd ed. Philadelphia/London: WB. Saunders Company; 1989. p. 290–318.

19. Anne-G, O. Hand book of neuroradiology. Mosby Year Book. 1991. p. 241–9.
20. Sutton D. A text books of radiology and imaging, vol. 2. 5th ed. Edinburgh/New York: Churchill Livingstone; 1980. p. 1499–577.
21. Post MDJ, Chan JC, Hensley GT, et al. Toxoplasma encephalitis in Haitian adult with acquired immune deficiency syndrome: clinical pathologic CT correlation. AJNR Am J Neuroradiol. 1983;140:861–6.
22. Krupp LB, Lipton RB, Swerdlow ML, et al. Progressive multifocal leukoencephalopathy: clinical and radiographic features. Ann Neurol. 1985;17:344–9.
23. Navia BA, Petito CK, Gold JWM, et al. Cerebral toxoplasmosis complicating the acquired immunodeficiency syndrome: clinical and neuropathological findings in 27 patients. Ann Neurol. 1986;19:224–8.
24. Post MJD, Tate LG, Quencer RM, et al. CT, MR and pathology in HIV encephalitis and meningitis. AJR Am J Roentgenol. 1988;151:373–80.
25. Poon T, Matoso I, Tcherthoff V, et al. CT features of primary cerebral lymphoma in AIDS and Non – AIDS patients. J Comput Assist Tomogr. 1989;13:6–9.
26. Spider WD, Simpson DM, Melson S, et al. Neurological complications of acquired immune deficiency syndrome: analysis of 50 patients. Ann Neurol. 1983;14:403–18.
27. Pinto AN. AIDS and cerebrovascular disease. Stroke. 1996;27(3):538–43.
28. Levy RM, Bredesen DE, Rosenblum ML. Neurological manifestation of acquired immune deficiency syndrome AIDS: a review of 200 cases. AJNR Am J Neuroradiol. 1986;7:833–9.
29. Coyle TE. Hematologic complications of human immunodeficiency virus infection and the acquired immunodeficiency syndrome. Med Clin North Am. 1997;81(2):449–70.
30. Harbol AW, Liesveld JL, Simpson-Haidaris PJ, Abbound CN. Mechanism of cytopenia in human immunodeficiency virus infection. Blood Rev. 1994;81(2):449–70.
31. Mugerwa RD, Marum LH, Serwadda D. Human immuno deficiency virus and AIDS in Uganda. East Afr Med J. 1996;73(1):20–6.
32. Mugyenyi P, Mugerwa R, Loughlin A et al. HIV-I seroprevalence and incidence in 3 Ugandan military cohorts over time. Conf Adv AIDS Vaccine Dev. 1996: Feb 11–15:299 (Poster 109).
33. Mugenyi P, Hom D, Loughlin A, Johnson J, et al. HIV-1 seroprevalence, incidence and risk behavior in the Ugandan military. Int Conf AIDS. 1996;11(1):139 (Abstract no Mo.C. 1483).
34. Wawer MJ, Sewankambo NK, Gray RH. Trends in crude prevalence may not reflect incidence in communities with mature epidemics. Int Conf AIDS. 1994;10(1):84 (Abstract No. 289 C).
35. Kangeya-Kayondo JF, Kamali A, Nunn AJ, et al. Incidence of HIV-Infection in adults and socio-demographic characteristics of sero converters in a rural population in Uganda: 1990–94. Int J Epidemiol. 1996;25:1077–82.
36. Nunn AJ, Wagner H, Okongo JM, et al. HIV-1 infection in a Uganda town of the trans-African highway: prevalence and risk factors. Int J STD AIDS. 1996;7(2):123–30.
37. De Cock K, Soro B, Coulibaly I, Lucas S. Tuberculosis and HIV infection in sub-Saharan Africa. JAMA. 1992;268:1581–7.
38. Wabinga HR, Parkin DM, Wabwire MF, Mugerwa JW. Cancer in Kampala, Uganda, in 1989–91: changes in incidence in the era of AIDS. Int J Cancer. 1993;54(1):26–36.
39. Safai B, Lynfield R, Lowenthal DA, et al. Cancers-Associated with HIV infection. Anti Cancer Reg. 1978;7:1055–67.
40. Centers for Disease Control. Update: acquired immune deficiency syndrome (AIDS) worldwide. MMWR Morb Mortal Wkly Rep. 1988;37:286–95.

Chapter 16
Neuropsychological Cases in a Low-Income National Referral Hospital

Janet Nakigudde

Abstract Neuropsychological assessment in Low and Middle Income Countries (LMIC) is clearly in its infancy. Often there are no neuropsychologists making it a big area of challenge for neuropsychology in the LMIC, especially in Africa, including Uganda.

This chapter will review cases of adult patients who suffered from cognitive deficits including dementia, that underwent psychometric assessment. However the tests that were done were limited showing a need to do more specific and comprehensive tests in order to ascertain the nature of dementias or other lesions which the different patients had. This calls for advanced training and obtaining the necessary testing tools as a means to advance the field of neuropsychology and assessment in Uganda.

Keywords Neuropsychology • Assessment • Dementia • Low and middle income country • Alcohol • Trauma • HIV/AIDS

Background

Neuropsychology is a discipline entity that is concerned with the way behavior is expressed in brain dysfunction [1]. It is a quantitative assessment of obtaining information regarding behavior and brain functioning. Whereas this discipline has evolved since the first and second World Wars in Europe and the US, it is a recent phenomenon in Africa and it is clearly in its infancy. In Sub-Sahara Africa, South Africa is the leading neuropsychology site but still with only a burgeoning specialty [2]. Elsewhere in the rest of Sub Saharan Africa as in most Low and Middle Income Countries (LMIC), neuropsychology is taught at university in the departments of Psychology but mainly as an elementary introduction course unit for the Masters

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S. Musisi, S. Jacobson (eds.), *Brain Degeneration and Dementia in Sub-Saharan Africa*, DOI 10.1007/978-1-4939-2456-1_16

programs in Psychology. As such not much is done in the way of assessing neuropsychological disorders, and rehabilitation of individuals of these disorders. Considering that Sub Sahara Africa has one of the highest prevalence of infectious diseases including HIV and its related neurological complications, and also that Africa has one of the highest alcohol consumption rates and subsequently high incidences of accidents there is a need to pay attention to this young discipline as a way of furthering management of neuropsychological/neuropsychiatric cases in these low income settings. Although Uganda has a relatively young population with over 50 % of the population comprising of children of 0–15 years, the country still has a population that gets into old age. This subsequently exposes the elderly to geriatric neuropsychological complications requiring assessment and rehabilitation.

Infections may affect behavior and brain functioning and it is well documented that HIV/AIDS will commonly manifest with neurological impairments [3]. Neuropsychological screening and assessment of HIV-infected patients will typically show cognitive deficits in psychomotor speed, attention and frontal lobe function as well as in verbal and non-verbal memory [4]. The following case report illustrates a typical patient with HIV neurological complications in the Ugandan setting.

HIV/AIDS Associated Dementia JB was a 74 year old male retired civil servant with an education level of 16 years. He was referred by a psychiatrist to a psychologist for psychometric assessment because of progressive forgetfulness and a change in his behavior. His wife reported that prior to the change in behavior, the patient was known to be financially responsible and would not carelessly spend his money. Collateral history showed that the patient was sexually and financially disinhibited at the time of referral. With changes in his behavior, the patient gradually became more and more extravagant and was progressively unable to account of how he was spending money. This caused a financial loss to the family and alarmed his wife. The patient was also easily suggestible and he would readily agree to other people's suggestions regarding his estate. This caused intense distress to the family because they feared that they would lose their property if he sold it. They wanted something to be done. JB had no previous psychiatric history and he did not abuse alcohol or drugs. Whereas he was previously a well kempt elderly man, he had stopped taking care of himself and would spend many days without bathing. He, however, readily took a shower whenever it was pointed out that he had not had a shower in a long time. He would also readily change into fresh clothes if this was also pointed out to him.

On cognitive testing, the patient was well oriented in time and place. He however did not perform as was expected for an individual with his academic background on attention and concentration. His performance on memory-recall was poor (0/5) and his recognition was average (5/7). His anterograde and retrograde memory were average (5/7 and 4/4) respectively. Verbally, the client performed averagely (4/7 and 4/7) respectively. He could comprehend instructions and his writing was still clear. When told to repeat words (immediate recall), the client was good at this task. He was also good at the naming and reading tasks. Long term memory was impaired. His visuo-spatial tasks were poorly done. However his perceptual abilities were

intact. The cognitive assessment coupled with the collateral history was suggestive of dementia. A recommended HIV serological test turned out positive but Syphilis serology was negative. As to whether this man also had an age-related dementia, such as Alzheimer's Dementia remains an unanswered question. This is a common dilemma in LMIC in this age group.

Intoxications are another common cause of brain damage calling for neuropsychological assessment. Chronic consumption of alcohol is often indicated in cognitive impairment in LMIC [5]. The following is an illustrative case of a patient that had been abusing alcohol and was referred to be cognitively assessed. It often occurs in middle aged males, younger than the age-related dementias.

Case A: Alcoholic Dementia PM was a 54 year old highly educated individual who was a Chief Executive Officer (CEO) of an international company. Collateral history from his wife indicated that he was progressively becoming forgetful. He could however still drive himself to his workplace. He had developed anxiety probably because he had realized that he was losing his memory and would often forget important things including job-related appointments. He was signing important documents without proper scrutiny of what was in the documents and his colleagues were concerned that this could lead to financial loss to the company if he continued working in his capacity as CEO. It is this pressure at work that was the reason for the referral for psychological assessment.

PM had overt memory loss as was evidenced by his lack of recognition of a son whom he had not seen in a year. His Activities of Daily Living, ADLs, were very compromised. He had challenges with dressing himself. He also had challenges with finding his way around the house that he had stayed in all his married life. He had challenges describing what he had had for breakfast that day. He had difficulties with both his long and short memories. He also had challenges with abstract reasoning and he commonly resorted to confabulating. His scores on the Wechsler Adult Intelligence Scale (WAIS) subtests were lower than expected for an individual of his level of education, socioeconomic status and age. On behavior observation, it was noted that he was not able to walk unaided and supported because he had developed an imbalance. His HIV and Syphilis serological status were negative and apart from his abusing alcohol there were no other reported explanations for his rapid progressive memory loss. It was not possible to do expensive investigations such as MRI and brain CT scan as he could not afford them and he had no health insurance. This would have complemented our findings. Such is a common scenario in LMIC, such as Uganda.

Case B SM was a 46 year old male who had been educated in the USA and was a lawyer. He was currently unemployed. He was referred because he was progressively becoming forgetful of where he would place his money and as such would complain that other people were taking his money. The client had no known physical illnesses and he appeared healthy. Although he denied that he was a regular alcohol user, his sister reported that while growing up, he (the client) always had a beer can! He had started abusing alcohol from a very early age in secondary school. On interviewing the client, he had challenges recalling where he had attended grad-

uate school. Whereas the patient performed well on the cognitive domains of fluency, and averagely on attention and orientation, language and visiospartial, he performed poorly on memory. The cognitive assessment was indicated that he had challenges with thinking and recall. He would confabulate responses when asked a question to which he could not recall the answer.

Age-Related Dementias With Behavioral and Psychological Symptoms of Dementis, BPSD These cases usually present in the elderly and often require neuropsychological assessment in the geriatric population. The following two cases are illustrative:

Case I BM was a 76 year old male with 11 years of formal education. He was married and was brought in by his daughter. He was referred for a psychological assessment because of impairment in his activities of daily living and wild accusations that he could hear strangers who came to his house in the night to make love to his 72 year old wife. The client had no known physical illness. He did not take alcohol or drugs. He had never had any previous psychiatric illness. He however realized that he had memory problems and whenever he was asked a question, he would ask his daughter to respond on his behalf. He was using his daughter as the device to help him fill in his memory gaps. On cognitive assessment, the client refused to make any attempts on drawing. The Addenbrooke's Cognitive Examination showed that he had challenges in areas of attention and orientation, language, visuospatial, fluency and memory. These were severe enough to impair the client's daily functioning. He also had fixed paranoid delusions and auditory hallucinations, accusing his wife of 50 years to be having affairs. Indeed he wanted to ask for a divorce to the chagrin of his already grown up children. Sometimes he would wake up in the middle of the night to go and beat off the strangers he complained of. He had dementia associated with the "Behavioral and Psychological Symptoms of Dementia, BPSD". We were not able to ascertain the nature of the dementia as he could not afford expensive investigations.

Case II YK was a 76 year old male who presented to the national referral hospital for assessment because of family disharmony and attempted suicide coupled with progressive memory loss. The client was well educated and held a post-graduate university degree. He was relatively a successful entrepreneur and administrator. Collateral history showed that there was a history of dementia on his paternal side. The client was hypertensive and he also had a hearing impairment. For several years, the patient would accuse his house help for wanting to poison him. Later he started accusing his wife for wanting to poison him. He began perceiving that everyone around him wanted to harm him and he had become highly suspicious. He would forget where he had placed his medications and would then accuse others of wanting him dead by hiding his medications. He also forgot where he had put (hidden) his money and then accused others of having stolen it. On observation, the client was slow in his movements but he had been very belligerent at the time he had been admitted to hospital and had been sedated. This could have been the reason for his apparent slow movement. He did not abuse alcohol or drugs and his physical

examination and laboratory tests were unremarkable. The brain CT and MRI scans had shown widespread cortical atrophy, more marked in the frontal and temporal lobe areas.

The patient was tested on a number of cognitive domains including executive functioning, attention, language, abstraction, delayed recall, orientation, memory and fluency. Using the Addenbrooke's cognitive examination the patient scored 51 out of a possible score of 100. With a cut off score of 82, this patient presented with dementia of a moderate degree of severity associated with Behavioral and Psychological Symptoms of Dementia, BPSD. A hearing aid was recommended as part of his treatment.In both cases I and II above, anti-dementia treatment had to be combined with family therapy interventions and medications to counteract the BPSD.

Neuropsychological assessment of children is even rarer and in many cases there are no child neuropsychologists. This remains a big area of challenge for neuropsychology in LMIC, especially in Africa, including Uganda.

Conclusion

Neuropsychological assessment in low income settings is clearly in its infancy. Although all the above cases indicate that the patients suffered from cognitive deficits and that they had dementia, there was still need to do more specific and comprehensive tests in regard to ascertain the nature of dementia which the different patients had. This calls for advanced training and obtaining the necessary measures and testing tools as well as equipment to complement the scant measures that are available in these low income settings.

References

1. Lezak MD, Howieson DB, Loring DW, Hannay HJ. Neuropsychological assessment. New York: Oxford University Press; 2004.
2. Lucas M. Neuropsychology comes of age. psySSA Psychological society of South Africa; 2011, Killarney, South Africa.
3. Sactor N, Nakasujja N, Skolsky RLS, Robertson K, Musisi S, Ronald A. HIV subtype D is associated with dementia compared with subtype A, in immunosuppressed individuals at risk of cognitive impairment in Kampala, Uganda. Clinical Infectious Disease. 2009;49(5):780–6.
4. Manji H, Miller R. The neurology of HIV infection. J Neurol Neurosurg Psychiatry. 2004;75:i29–35, Bethesda, MD. doi:10.1136/jnnp.2003.034348.
5. Oscar-Berman M. Neuropsychological vulnerabilities in chronic alcoholism. In: Noronha A, Eckardt MJ. Warren K, editors. Neuroscience and behavioral research portfolio. National Institute on alcohol abuse and alcoholism; (2000). p. 437–71.

Part V
Biological, Neurological, and Psychiatric Findings: Case Reports of Brain Degenerations at Mulago Hospital, Uganda

Chapter 17
A Case of Alzheimer's Dementia in Uganda

Justine Diana Namuli

Abstract Literature on the prevalence of dementia and its different types in Uganda is scanty. In the Ugandan clinical setting, in addition to Alzheimer's disease and the vascular dementias, the other common causes of dementia include infections (commonly HIV and Syphilis), substance abuse (alcohol), trauma (road traffic accidents) and nutritional deficiencies (vitamin B-12). Uganda has a population of about 35 million people, with life expectancy at birth of the total population is at 53.45 years, which puts her at 204th in the world. About 2.1 % of the total Ugandan population is over 65 % and 4.6 % is over 60. These figures are expected to rise, but as it is, the epidemiological data may not necessarily follow world trends due to the prevalence of other killer diseases notably HIV/AIDS. A Ugandan study found that 13.2 % of all elderly patients of >60 years admitted on non-psychiatric wards had dementia followed by depression as the two most common psychiatric diseases of the elderly. In keeping with WHO recommendations for Low and Middle Income Countries (LMIC) with young populations, the cut off age to be considered elderly is ≥60 years in Uganda. This chapter presents a case of Alzheimer's Dementia illustrating the challenges of care and management of this disease in a Ugandan African setting.

Keywords Alzheimer's disease • Dementia • Activities of daily living • Care • Behavioral and Psychological Symptoms of Dementia (BPSD) • Anticholinesterase inhibitors

Abbreviations

AD	Alzheimer's Disease
ADL	Activities of Daily Living
BPSD	Behavioral and Psychological Symptoms of Dementia
CT	Computerized Tomography
EKG/ECG	Electrocardiogram

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S. Musisi, S. Jacobson (eds.), *Brain Degeneration and Dementia in Sub-Saharan Africa*, DOI 10.1007/978-1-4939-2456-1_17

HIV	Human Immunodeficiency Virus
MMSE	Mini Mental State Examination
MRI	Magnetic Resonance Imaging
UBOS	Uganda Bureau of Statistics

Introduction

Dementia is a progressive impairment of cognitive functioning of the brain occurring in clear consciousness. It is a common manifestation of brain degeneration from a variety causes, but occurs mostly in old age. Dementia consists of a variety of symptoms that suggest chronic and widespread cognitive dysfunction. Global impairment of intellect is the essential feature, manifested as difficulty with memory, attention, thinking and comprehension. Other mental functions can often be affected, including personality, mood, judgment, perception and behavior [1]. All dementias have certain common elements that result in significant impairment in social or occupational functioning and cause a significant decline from a previous level of functioning. The disorder can be progressive or static, permanent or reversible. The reversibility of dementia is related to the underlying pathological condition and to the availability and application of effective treatment.

According to the 2002 World Health Organization report, the number of people with dementia worldwide is expected to double to 65.7 million in 2030 and more than triple to 115.4 million by 2050. This is partially explained by the general increase in life expectancy globally. More people are now expected to live beyond the age of 60. As it is, dementia unfortunately targets these demographics and therefore the projected increase in its prevalence is not at all unexpected.

The most common type of dementia is Alzheimer's dementia which accounts for 50–60 % of all dementias [1]. The second most common type of dementia is vascular dementia, which is causally related to cerebrovascular disease especially hypertension. Vascular dementias account for 15–30 % of all dementias. Vascular dementia is most common in persons between the ages of 60 and 70 and is more common in men than in women. Approximately 10–15 % of patients have coexisting vascular dementia and dementia of the Alzheimer's type, otherwise called mixed dementia [1].

Other causes of dementia each represent 1–5 % of all cases and they include head trauma, alcohol-related dementias and various movement disorder-related dementias, such as Huntington's disease and Parkinson's disease [1]. Because dementia is a fairly general syndrome, it has many causes, and clinicians must embark on a careful clinical workup of a patient with dementia to establish the cause.

The prevalence of dementia and its different types in Uganda is scanty. In the Ugandan clinical setting, in addition to Alzheimer's disease and the vascular dementias, the other common causes of dementia include infections (commonly HIV and Syphilis), substance abuse (alcohol), trauma (road traffic accidents) and nutritional deficiencies (vitamin B-12). Uganda has a population of about 35 million people,

with life expectancy at birth of the total population at 53.45 years, which puts her at 204th in the world [2]. About 2.1 % of the total Ugandan population is over 65 years old [3]. These figures are expected to rise, but as it is, the epidemiological data may not necessarily follow world trends. A Ugandan study found that 13.2 % of all elderly patients of >60 years admitted on non-psychiatric wards had dementia [4]. In keeping with WHO recommendations for Low and Middle Income Countries (LMIC) with young populations, the cut off age to be considered elderly is ≥60 years in Uganda.

Alzheimer's Disease (AD)

First described in 1907 in a 51-year-old woman by Professor Alois Alzheimer, Alzheimer's disease (AD) is one of the top ten leading causes of death in the United States [5]. It is the sixth leading cause of death among American adults, and the fifth leading cause of death for adults aged 65 years and older [5]. An estimated 5.4 million Americans have Alzheimer's disease. This number has doubled since 1980, and is expected to be as high as 16 million by 2050 [6]. In 2011, the total Medicare and Medicaid spending for individuals with AD was estimated at $130 billion [7].

Gender differences in the incidence rates of AD indicate women to have a higher risk of developing AD particularly in the population older than 85 years [8]. Conservative estimates suggest that 1 in 20 persons age 65 and older, 1 in 4 persons age 80 and older, and half of persons age 95 and older have Alzheimer's disease [9]. Thus after age of 65 years when the prevalence is 5 %, the prevalence of AD increases by 1 % for every year lived. In Africa, little has been done to estimate the prevalence of AD in the general population. In a study of elderly patients attending psychiatric services at Mulago National Referral hospital in Uganda, dementia was second to depression as the most common reason for seeking psychiatric care amongst the elderly [10].

Below is a case of Alzheimer's dementia that presented to the Uganda National referral Mulago Hospital Mental Health clinic on police request, following a land dispute.

Case Report of Alzheimer's Dementia

S.N. was a 69 year old Ugandan married man from Kampala district of Uganda. He worked as a Muslim cleric, who taught religious studies for a job. He had previously been a businessman before retiring into religious teaching. He was married with six wives and 25 children.

He presented to the Mental Health Clinic in Mulago Hospital on 12/3/2010 accompanied by his daughter, a psychiatric nurse, with complaints of forgetfulness for 1 year, signing land-sale documents he couldn't remember, and feeling sad for

more than 2 weeks. The history was taken collaterally from his daughter as he, himself, could not give a good account of himself.

In the previous 1 year before presentation to hospital, S.N. had become increasingly forgetful. This begun with forgetting such common things as names of people including his relatives, his children and close friends and it progressed to forgetting important religious events, including his dutiful religious recitation prayers, despite being an Islamic preacher. He often failed to pick his change from grocery stores, often left bought items behind in shops and was unable to calculate his money. S.N. was seen to have progressively worsened in his memory to the point that he transacted a sale of his land, relinquishing it together with its accompanying documents but later he neither remembered the sale nor the buyer and he denied having ever sold his land, prompting the buyer to report and file a court case against S.N. to the police. Three months prior to this consultation, S.N. was reported to have wandered away from home, got lost and failed to trace his way back home, only to be picked up by a good Samaritan who brought him back to his home.

S.N's previous psychiatric history was unremarkable, with no psychiatric illness whatsoever in the past nor any psychiatric admissions or treatments. He neither used alcohol nor drugs of abuse. He was physically healthy with no hypertension and no diabetes mellitus. He had no history of sudden falls or trauma to his head. He had no history of seizures or headaches.

He was married to six wives but currently three had left. He had 25 children but he would no longer identify them all. He had a son with bipolar affective disorder. There was no history of dementia in his family.

Prior to the onset of AD, S.N. was an outgoing, social, active religious person with many friends. He was described as hardworking and a successful businessman. His hobbies included visiting people and listening to radio for news and world happenings. He had only one previous history of involvement with the law in the land matter which had caused a dispute and this was the main reason police referred him for psychiatric assessment.

The initial Mental State Examination showed an elderly gentleman, dressed appropriately in traditional Ugandan attire (kanzu). He was well groomed and was in fairly good nutritional state. His speech was labored in search of words and he seemed to refer most of the questions to his daughter for answers. There was no thought disorder and no perceptual disturbances elicited. He was alert and fully conscious; however, he was disoriented in time, place and person. He could not sustain attention and his concentration was equally impaired. He had intact immediate registration in memory, but 5-min recall, intermediate, short term and long term memories were all impaired as he could not recall ideas discussed at the beginning of the interview, and recent and past events in the country did not seem to mean anything to him.

His judgment for safety, social and abstraction were all impaired as he could not clearly explain how to get out when faced with danger, could not maintain social etiquette and could not interpret simple and common proverbs. He lacked insight into his illness.

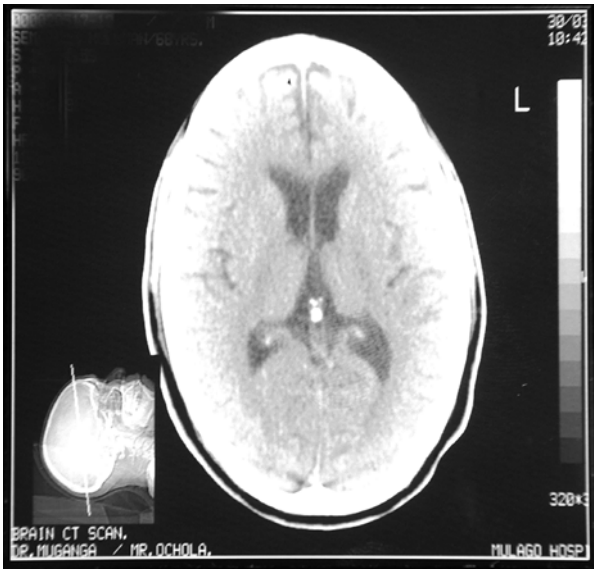

Fig. 17.1 Image of S.N.'s brain CT scan

Investigations included the Mini Mental Status Examination, MMSE, where he scored 9/30. He had negative serology for HIV and Syphilis. He had normal values for Complete Blood Count, serum vitamin B-12, liver, thyroid and renal function tests as well as normal lipid profile and cardiac function by echocardiography and EKG.

S.N.'s brain CT scan showed features suggestive of brain atrophy, most prominently in the fronto-temporal areas (Fig. 17.1). His brain CT Scan report read:

> The Lateral and 3rd ventricles are widened. The 4thVentricle is normal. The ambiens and basal cisterns are normal. The Sylvian fissures are prominent. The midbrain, cerebellum are normal There is sulcial widening of =11 mm. Features are suggestive of Brain Atrophy more marked in the Frontal and Temporal lobes.

A diagnosis of Alzheimer's dementia complicated by depression was made. S.N.'s biological management included administering the cholinesterase inhibitor Donepezil and the antidepressant Imipramine. Social management involved psychoeducation of the family about the nature of AD illness, its course and prognosis and how to care for him including Activities of Daily living (ADL)

At 1 month follow up S.N. reported improved sleep and mood and the antidepressant of Imipramine was later withdrawn after a few months. However, the memory was still impaired. He later developed behavioral and psychological symptoms of dementia (BPSD), which included wandering away from home, talking to himself, easily getting irritated and wanting to strike out. Risperidone was added to his treatment with good effect. Later memantine was added to the Donepezil as the two anti-dementia cholinesterase inhibitor drugs of choice in the maximum recommended dosages. However compliance with medication was a problem because of

the use of alternative herbal medicine as suggested by his relatives who were alarmed by his progressive deterioration. At his last clinic visit he had been off the prescribed drugs for 4 months, and his memory was grossly impaired. He was stammering grossly in his and his ADLs had deteriorated necessitating more assistance in his daily care. At times he would urinate in presence of his grandchildren and had to be assisted for dressing, although he could feed and bathe himself. S.N died 3 years after diagnosis of AD.

Discussion

This is a case of Alzheimer's dementia with typical clinical presentation. This patient reportedly developed symptoms at the age of 68 years which falls in the age range of onset of Alzheimer's disease. For over a year, impaired memory was his first symptom and it went on deteriorating. He delayed seeking medical attention because family members thought his memory problems were associated to normal aging. He was involved in a police case after selling his land and denied the purchaser to access it, yet he acknowledged receipt of money and even had the signed land documents. This made the family realize that he could be having a problem of memory and comprehension.

In a Ugandan clinical setting, like in all low income countries, there is a limitation on biological investigations. For example we could not do MRI-scans. Alzheimer's dementia is thus often a clinical diagnosis based on exclusion.

Legal complications often come in AD and often this poses legal wrangles for example whether this gentleman was in his rightful mind at the time he sold his land, or whether he was having a lucid interval. One usually has to rely on family understandings and agreements. In this case, the matter was resolved later between the family and the land purchaser who returned the money, and the family obtained their land.

In Africa, including Uganda, people have a culture of seeking alternative modes of treatment once they are diagnosed with chronic unrelenting illnesses with no medical cure. In this patient the family members resorted to use of traditional herbal medicine when they realized that their relative was diagnosed with an incurable disease. Sometimes, relatives often invoke witchcraft.

The cost and burden of care for AD can be staggering. In western countries, for example USA, over 15 million Americans provide unpaid care for persons with Alzheimer's disease or other dementias [7]. Such services, including Nursing homes for the aged, lack in developing countries. The unpaid caregivers are primarily family members, hence causing a heavy care burden to family and friends. However, traditional African cultural systems are fast disappearing and the extended family system has been extended to its limits due to changes to a cash economy and it no longer holds. Yet, there are no social or government agencies for the care of the old and demented. Thus in Uganda, as a country, care of the elderly demented is thus a challenge and it is mostly done by family just as this patient was being taken care of

by the daughter. Over 80 % of the care for the elderly demented is provided at home by family caregiver. Fewer than 10 % of older demented adults receive their care from paid workers [11]. Caring for a person with Alzheimer's dementia or other dementias is often very difficult, and many family and other unpaid caregivers experience high levels of emotional stress and depression. Time spent on caregiving often has a negative impact on health, employment, income and the family finances [12].

The good prognostic factors in this patient were there being no family history of dementia and no history of cardiovascular disease, hence rules out a possibility of mixed vascular and Alzheimer's dementia. He did not use alcohol or abuse drugs and he had the daughter's support.

The poor prognostic factors included early age of on set, poor adherence to prescribed treatment as the family preferred using traditional herbal medicine. The patient had no insight into his illness, had on and off Behavioral and Psychological Symptoms of Dementia and his memory was deteriorating fast. Thus overall, the prognosis was poor as happens in most cases of AD.

Conclusion

There is a need for health care professionals even in developing countries, to be trained in geriatrics. Old age is escalating, but with few healthcare providers. Geriatric services should be incorporated at all levels of health care. This calls for more research and funding in this growing area of medicine.

References

1. Kaplan HI, Sadock BJ. Dementia. Synopsis of psychiatry-behavioral sciences/clinical psychiatry. 10th ed. Philadelphia: Lippincott Williams and Wilkins; 2007. p. 329–30.
2. National Population Policy for Social Transformation and Sustainable Development. Population Secretariat, Ministry of Finance, Planning and Economic Development. Government of the Republic of Uganda. http://www.popsec.org. 2008.
3. Uganda Bureau of Statistics (UBOS). Statistical abstract. Government of Uganda, Kampala, Uganda. www.opendev.ug/resources/2012-statistical-abstract-ubos. 2012.
4. Nakasujja N, Musisi S, Walugembe J, Wallace D. Psychiatric disorders among the elderly on non-psychiatric wards in an African setting. Int Psychogeriatr. 2007;19:691.
5. Miniño A, Murphy SL, Xu J, Kochanek K. Deaths: final data for 2008. National Vital Statistics Reports. Hyattsville: National Center for Health Statistics; 2011.
6. Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA. Alzheimer disease in the U.S. population: prevalence estimates using the 2000 census. Arch Neurol. 2000;60(8):1119–22.
7. Bynum J. Medicare current beneficiary survey 2011- accountable care organization: lessons from current practice. The Dartmouth Institute for Health Policy and Clinical Practice, Lebanon. www.academyhealth.org/files/2009/sunday/bynumjl.pdf.
8. Di Carlo A, Baidereschi M, Amaducci L, Lepore V, Bracco L, Maggi S, Perissinotto E, Scarlato G, Farchi G, Inzitari D, ILSA Working Group. Incidence of dementia, Alzheimer's disease, and vascular dementia in Italy. The ILSA Study. J Am Geriatr Soc. 2002;50(1):41–8.

9. Moore MJ, Zhu CW and Clipp EC: Informal costs of dementia care: Estimates from the national long-term care register study. The Journal of Gerontology, Series B. 2000;56(4): 219–228.
10. Musisi S, Nakasujja N, Byakika-Kibwika P, et al. Psychosocial and diagnostic profiles of elderly patients attending outpatient psychiatric care at Mulago Hospital Uganda. African Association of Psychiatrists and allied professionals annual conference; 2008 June 18th–20th; Accra; 2008.
11. Institute of Medicine. Retooling for an aging America: building the health care workforce. Washington, DC: The National Academies Press; 2008.
12. Alzheimer's Association: The 2012 Alzheimer's Disease Facts and Figures Report. Proceeds of the Alzheimer Association conference, Monterey, California, USA. March 22, 2012. www.alz.org/downloads/facts_figures_2012.pdf.

Chapter 18
A Case Report of Mania and Glioma

Nolbert Gumisiriza

Abstract It is well established that many physical illnesses either present as or have a component of neuropsychiatric symptoms. Moreover, due to cultural or social influences, patients may present their psychiatric illness in form of somatised physical symptoms. It becomes a diagnostic challenge when a patient presents with concurrent primary psychiatric illness and concurrent organic brain disease. Such a scenario is not uncommon in brain degenerative disorders where Central Nervous System malignancy often causes diagnostic confusion when accompanied by psychiatric symptoms. This chapter discusses a case of a patient who, for a long period, was managed for a mood disorder and later discovered to be having a temporo-parieto-frontal brain mass. The patient was a 32 year old female, with a sporadic history of a mood disorder for the past 13 years characterized by episodes of mania and depression. Her first manic episode was at 19 years of age which was treated successfully with antipsychotics and mood stabilizers at a mental institution. She then developed severe but intermittent right sided headaches which were later associated with photophobia and blurred vision but no vomiting, no postural changes and no cognitive or convulsive symptoms. Subsequent CT and MRI scan examinations revealed a right-sided temporo-parieto-frontal brain mass which was successfully surgically resected although she continued to need her psychotropic medications for mood stabilization.

Regardless of how small the statistical numbers are, brain tumors occur and are on a gradual increase in Africa, representing an aspect of potentially curable brain degeneration if caught early. It is therefore highly recommended that neuroimaging be carried out in the following cases: all patients with an index psychiatric episode especially of late onset (>30 years), patients with atypical presentations, patients with psychiatric presentations accompanied by specific neurologic or neurobehavioral changes and patients with poor response to psychopharmacologic treatment.

Keywords Mood disorder • Brain tumor • CT and MRI scan • Mood stabilizer • Headache • Mania • Depression

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S. Musisi, S. Jacobson (eds.), *Brain Degeneration and Dementia in Sub-Saharan Africa*, DOI 10.1007/978-1-4939-2456-1_18

Introduction

It is well established that many physical illnesses either present as or have a component of neuropsychiatric symptoms [1]. Due to cultural or social influences, patients may present their psychiatric illness in form of somatised physical symptoms. It becomes a diagnostic challenge when a patient presents with concurrent primary psychiatric illness and conditions directly affecting the brain. Such a scenario is not uncommon in degenerative disorders of the brain. Central Nervous System malignancy is one form of brain degeneration that often causes diagnostic confusion when it presents with psychiatric symptomatology. This chapter discusses a case of a patient who, for a long period, was managed for a mood disorder and later discovered to be having a temporo-parieto-frontal brain mass. The case posed questions as to whether her psychiatric symptoms were caused by the brain tumor or she developed the tumor at a later stage of a primary psychiatric illness.

Cancer is a steadily increasing concern in the African region. A report by WHO estimated that worldwide, 680,000 adults succumbed to cancer in 2008, a number that is greater than the combined deaths of Tuberculosis, Malaria, HIV and AIDS in that year. Over 70 % of these deaths occurred in developing countries [2]. The most common types of cancers registered in Uganda are cervical cancer (22 %), Kaposi sarcoma cancer (19 %) and breast cancer (13 %) in adult females while in adult males, the figures are; Kaposi sarcoma (29 %), prostate cancer (12 %) and Non Hodgkin's lymphoma (10 %) [2, 3]. Brain and central nervous system cancers are not so common worldwide and this remains the trend in Uganda with a prevalence of 0.5 % in males and 0.6 % in females of all registered cancers [3].

Brain tumors can originate in the brain itself (primary brain tumors) or involve the brain as a metastatic site mostly from lungs or breasts (secondary brain tumors). In general, symptoms of brain tumors may include: recurring or persistent dull headaches, vomiting, dizziness, seizures, photophobia, weakness or paralysis in a part of the body, changes in sensory perceptions like vision and hearing and changes in personality and/or thought processes. The latter often gets confused with primary psychiatric illness. Sometimes, brain neoplasms are mimicked by intracranial space occupying lesions like abscesses, cysts, arteriovenous malformations, aneurysms, cerebral hemorrhage, subdural hematomas, sarcoidosis, tuberculomas, other granulomas and parasites.

Up to 50 % of patients with brain tumors reportedly have manifestations of a psychiatric nature [4]. Patients can present with depression, mania, psychosis, anxiety, apathy, cognitive or personality changes, and even anorexia nervosa [5]. Several factors influence the nature of neuropsychiatric symptoms exhibited by the tumor. These include: the location of the tumor in the brain, extent of tumor involvement, the rapidity of its growth, its propensity to cause increased intracranial pressure, the patient's premorbid psychiatric history, level of functioning, and characteristic psychological coping mechanisms [6]. Even with recent vast knowledge in the area of neuropsychiatry, it has not been possible to precisely predict relations between tumor location or histological type and the likelihood of mental sequelae. Important to note

is that management of brain lesions which often includes surgery, chemotherapy, steroids and radiotherapy can also cause secondary psychiatric symptoms. Among the common neuropsychiatric manifestation of brain malignancy is mania.

To diagnose a manic episode, a patient must experience irritability or euphoric mood, with three (if euphoric) or four (if irritable) of seven cardinal symptoms of mania, for 1 week [7]. These cardinal symptoms are: distractibility, insomnia, grandiosity, flight of ideas, an increase in goal-directed activities, pressured speech and thoughtlessness or dysfunctional pleasure -seeking activities which do not display usual judgment. These symptoms must cause significant social or occupational dysfunction [7].

The worldwide life time prevalence of mania or Bipolar Affective Disorder is approximately 1 % with no significant differences between males and females [8]. In Uganda, prevalence of mania is about 1.6 % [9]. Mania has many etiologies with the most common being primary mania as one phase of bipolar affective disorder, whereas secondary mania may results from pharmacological, metabolic, infections, neoplastic or neurologic causes like brain occupying lesions [8]. The etiology of mania is important because although acute symptomatic treatment of both primary and secondary mania may be similar, appropriate treatment of secondary mania includes addressing the cause.

The following case report is illustrative of these conditions.

Glioma Ad Mania: A Case Report

SK was a 32 year old female from Kampala, the capital city of Uganda, who ran her own restaurant. She had had a sporadic history of a mood disorder for the past 13 years characterized by episodes of mania and depression. Her first manic episode was at 19 years of age which was treated successfully with antipsychotics at a mental institution. This was followed by a 10 year period of being symptom free while off medication. Two years prior to the current presentation, she had had multiple manic relapses followed by depression necessitating her being started on mood stabilizers (lithium carbonate) and antipsychotics (Risperidone).

One week prior to the presenting episode, SK had experienced poor sleep, restlessness, irritability and would work at her restaurant without rest until the late hours of the night. She had also experienced 3 days of persistently severe right sided headaches which were associated with photophobia and social withdrawal but without vomiting, neck stiffness or fevers. She denied any perceptual symptoms and claimed to not having used alcohol or other drugs and substances. There was no known past history of head trauma or seizures. The severity of her headache prompted the family to bring her to hospital.

SK had, for the previous 2 years, experienced severe but intermittent headaches which were usually right sided but not associated with photophobia, vomiting, blurred vision or postural changes. She started putting on spectacles as a result of developing headaches while reading. These headaches were usually treated as migraines with various analgesics and they would improve.

She had had a normal childhood and schooling, did not abuse drugs or alcohol and she was a religious and reserved person. On these past admissions, she did not present any perceptual disturbances and had neither seizures nor history of head trauma. Her father, who had 36 children from 6 wives, had passed away 3 years previously of melanoma. Her paternal uncle and cousin had disappeared from home without a trace. She also had a step brother who was dependant on alcohol.

The mental status examination at time of admission showed a young lady who was obese, jocular, and talkative, with ptosis of right eye and left sided body weakness. Her speech was dysarthric but connected. Her mood was labile. The thoughts were normal but with pre-occupation with complaints of her headaches. There was no grandiosity and no perceptual disturbances. Her cognition was intact. She had full insight regarding her bipolar disorder.

Significant physical examinations were; normal temperature, blood pressure of 170/100 mmHg, pulse rate of 76 beats/min, body weight of 92 kg and BMI of 32. Neurological examination showed an alert and fully oriented lady, Glasgow Coma Scale of 14/15, pupils were equal and reactive to light and accommodation, Kerning's sign was negative, muscle tone and reflexes were normal. She had a mild left sided hemiparesis.

Investigations which were carried out included the following:

- Laboratory: Fasting blood sugar = 7.9 mmol, Complete blood count showed a leucocytosis-14.39×10^9(NR 4–11×10^9cells), neutrophils 70 %, monocytes 7.6 % (NR 0.2–1 %). No Malaria parasites. Lipid profile, thyroid function test, C-reactive protein and urinalysis were all normal. Thyroid Function Tests were normal. HIV and Syphilis serology were negative.
- Radiological: Brain MRI scan revealed Intra-axial marked heterogeneous enhancement, complex cystic and solid mass with intratumoral hemorrhage and compressed brainstem in right temporal and occipital lobes. The radiologist came to the conclusion of a possible high grade glioma to rule out metastases (Fig. 18.1).

In order to exclude metastases in other areas, a chest x-ray, mammogram and abdominal-pelvic ultra sound scan were done and all were found normal.

A working diagnosis of Bipolar Affective Disorder, hypomanic phase with organic brain disease (brain tumor) plus syndrome X was made.

Treatment

- Neuropsychiatric symptoms were treated and stabilized with Risperidone 2 mg OD, Carbamazepine 400 mg B.I.D, Acetazolamide 250 mg Q.I.D, Mannitol 100 mg Q.I.D and Dexamethazone 4 mg T.I.D
- Diabetes mellitus and Hypertension were controlled with: Amilodipine 10 mg OD, Losartan-H 6.25 mg OD, Artrovastatin 10 mg OD, Piosafe 1 tablet pre-breakfast and pre-supper, soluble insulin 5–20 I.U depending on the blood glucose levels.

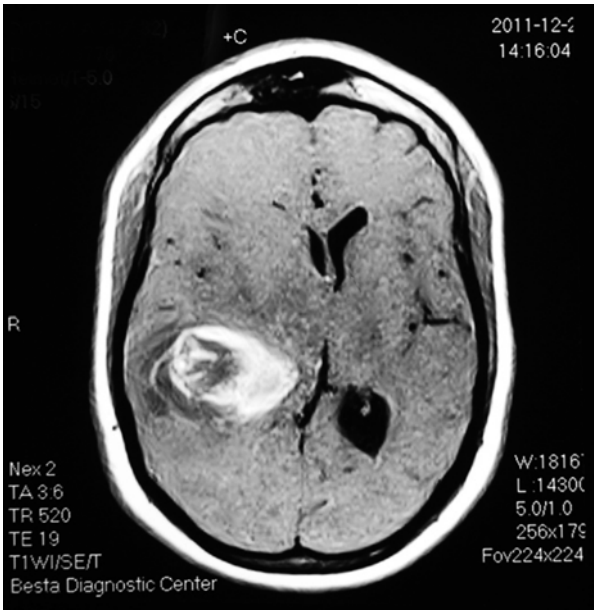

Fig. 18.1 Image of SK's brain MRI

SK's family requested that she gets referred abroad for a second opinion and treatment. After 2 weeks of admission, the patient's psychiatric symptoms had improved and she was transferred to India for further treatment after consultation with an oncologist. Management of SK in India involved tumor excision surgery. Pathological studies of excisional biopsy showed Fibrillary astrocytoma of the right parieto-occipito-temporal lobe.

The post surgical period of SK was characterized by a 2 months period of remission of her psychiatric and lateralizing neurological symptoms. However, twice from the time of surgery, she had had two admissions in a mental health facility with manic symptoms which have now stabilized for 2 years on mood stabilizers. Her previous and regular medications of mood stabilizers had been maintained throughout this entire period. SK continues to enjoy good mental and physical functioning on medication and follow up monitoring post-surgically.

Discussion

This case demonstrates the diagnostic challenges and dilemmas usually faced in resource constrained facilities of this world where patients often present with complex physical (CNS) and psychiatric disorders. One wonders whether this was a case of a brain tumor that was not diagnosed earlier, manifesting with psychiatric symptoms, or merely a coincidental misfortune of having both a brain tumor and a primary psychiatric condition at the same time.

In this particular case, SK had suffered from a manic episode at 19 years of age. She was treated and went on to live normally off medication for the next 10 years. When these manic symptoms resurfaced 10 years later, it was evident that her mental illness had become less responsive to medication, with her symptoms recurring more frequently. This is the period that her headaches become more severe and frequent. Perhaps this could have been the result of now an enlarged tumor that was not caught early at onset.

The brain imaging (brain CT scan and MRI) was carried out 2 years following constant complaints of headaches, when it became apparent that she had developed lateralizing neurological symptoms and photophobia. The imaging showed a right temporo-parieto-frontal brain mass.

Following the brain tumor removal, SK went into remission for 2 months but was however later admitted twice in a mental health facility after experiencing hypomanic episodes. She was maintained on mood stabilizer medication throughout this period. The fact that SK continued having manic episodes even after the removal of her brain tumor adds more weight to the thought that she may have had a primary psychiatric illness exacerbated by the coincidental brain tumor. However, it may be that the pressure effects of the now removed tumor may not have fully subsided till enough time had passed. Without prior brain imaging to rule out a slow growing tumor, all this contemplation unfortunately remains but educated theorization.

Conclusion

Regardless of how small the statistical numbers are, brain tumors occur and are on a gradual increase in Africa, representing an aspect of potentially curable brain degeneration if caught early. More relevant to the field of psychiatry, neuropsychiatric symptoms more often than not are part of the symptomology or sometimes even the presenting complaints. There should be a high index of suspicion when a patient complains of headaches that are persistent and increasing in severity or frequency, often associated with nausea, vomiting and photophobia. Focal neurological signs and symptoms and other sensory changes may be present. Unexplained changes in personality or cognitive functioning and onset of seizures, especially of new onset in an adult are an ominous sign.

Neuroimaging remains the most adequate method of identifying brain lesions. It is therefore highly recommended that neuroimaging be carried out in the following cases: all patients with an index psychiatric episode especially of late onset (>30 years), patients with atypical presentations, patients with psychiatric presentations accompanied by specific neurologic or neurobehavioral changes and patients with poor response to psychopharmacologic treatment.

References

1. Price TRP, Goetz KL, Lovell MR. Neuropsychiatric aspects of brain tumors. In: Yudowfsky SE, Hales RE, editors. The American Psychiatric Publishing textbook of neuropsychiatry and clinical neurosciences. 4th ed. Washington, DC: American Psychiatric Publishing; 2002. p. 753–81.
2. World Health Organization. National cancer control programs: policies and managerial guidelines. Geneva: WHO; 2002.
3. Wabinga HR, Parkin DM, Wabwire-Mangen F, Nambooze S. Trends in incidence in Kyadondo County, Uganda, 1960–1997. Br J Cancer. 2000;82:1585–92.
4. Madhusoodanan S, Danan D, Brenner R, Bogunovic O. Brain tumor and psychiatric manifestations: a case report and brief review. Ann Clin Psychiatry. 2004;16:111–3.
5. Jarquin-Valdivia AA. Psychiatric symptoms and brain tumors. Arch Neurol. 2004;61: 1800–4.
6. Krauthammer C, Klerman GL. Secondary mania: manic syndromes associated with antecedent physical illness or drugs. Arch Gen Psychiatry. 1978;35:1333–9.
7. APA. Diagnostic and statistical manual of psychiatric disease. 4th ed. (DSM-IV). Washington, DC: American Psychiatric Press; 1994.
8. Chow TF, Cummings JL. Neuropsychiatry: clinical assessment and approach to diagnosis. In: Sadock BJ, Sadock VA, editors. Comprehensive textbook of psychiatry, vol. 1. 7th ed. Baltimore: Williams and Wilkins; 2000. p. 1169–98.
9. Odokonyero R. Prevalence and associated factors of Axis I psychiatric disorder presenting at the Accident and Emergency department of Mulago hospital. Masters of Medicine in psychiatry dissertation, Makerere University; 2011.

Chapter 19
Secondary Mania of HIV/AIDS

Emmanuel Kiiza Mwesiga

Abstract Mania has for long been associated with HIV/AIDS and in many cases acts as a barrier to attaining best treatment outcomes in patients both conditions. Like many psychiatric disorders, mania was initially thought to be a psychological reaction to having HIV infection. Subsequent research has now proven that psychiatric disorders including mania could arise from the direct effects of HIV disease on the brain. Indeed research has shown secondary mania of HIV/AIDS to be different from primary mania in terms of clinical presentation, course, management and prognosis. This chapter deals with HIV mania and how it presents in the Ugandan setting. A case report helps to highlight these points. HIV mania and secondary mania of HIV/AIDS are used interchangeably in this chapter.

Keywords HIV/AIDS • Secondary mania • People living with HIV/AIDS (PLWHA)

Abbreviations

DSM IV TR	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revised
GCS	Glascow Coma Score
HAART	Highly Active Antiretroviral Therapy
ART	Antiretroviral Therapy
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome
PLWHA	People Living with HIV/AIDS

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S. Musisi, S. Jacobson (eds.), *Brain Degeneration and Dementia in Sub-Saharan Africa*, DOI 10.1007/978-1-4939-2456-1_19

Introduction

Mania or manic episodes have been described for centuries. The earliest descriptions of mania can be found as far back as in the Old Testament texts of the Christian bible. In many societies all over the world, accounts of mania go back centuries. HIV/AIDS, on the other hand, is a relatively new disease with the first cases first described in the early 1980s [1]. Both diseases however have the ability to bring about a lot of despair and suffering and are often stigmatized. HIV/AIDS, for example, has been one of the greatest health challenges of Sub-Saharan Africa for the last 30 years. In this time the disease has claimed over 15 million lives, devastated economies, families and the region as a whole with billions of dollars being spent in trying to curb the scourge [2].

Early in the pandemic it was noted that mental health disorders were closely related with HIV/AIDS with many psychiatric disorders having increased prevalence in HIV positive populations [2, 3]. People living with HIV/AIDS (PLWHA) have been found to be at a greater risk of having a psychiatric illness in the same way people with psychiatric disorders are at a higher risk of contracting HIV/AIDS [3, 4, 5].

The majority of the described HIV related mental disorders are affective disorders including mania and depression. However, HIV-associated neurocognitive disorders, HAND, are increasingly being documented. Many of the psychiatric disorders in HIV/AIDS have thus been studied and it is now becoming clearer that these conditions are not just psychological reactions to having the disease but are sequalae of the neuropathogenesis of HIV/AIDS.

With the introduction of Highly Active Antiretroviral Therapy (HAART), people living with HIV/AIDS are able to live longer lives and have improved livelihoods. Current studies however show that mental conditions are in some ways responsible for failure to reach desired targets especially in the area of condom use and drug adherence [6]. Various studies have shown worse outcomes in HIV/AIDS patients that are co morbid with mental disorders. Early diagnosis and treatment of metal disorders in HIV/AIDS is one of the ways in which meeting treatment goals especially in areas of adherence and condom use can be attained.

Primary Mania Versus Secondary Mania

Classification of mood disorders has changed over time through improvements in case definitions and scientific breakthroughs. From [7] who defined manic depressive illness to the unipolar- bipolar classification by [8] or the spectrum of affective disorders by Akiskal, the classification of affective disorders has kept on getting broader and better defined [9].

Today DSM IV TR [10] provides the standard for classification of mood disorders. The proposed DSM IV TR classification of mood disorders is listed in the table below (see Table 19.1).

Table 19.1 DSM IV classification of mood disorders

Major depressive disorders
Dysthmic disorder
Depressive disorders not otherwise specified
Bipolar 1 disorder
Bipolar II disorder
Cyclothymic disorder
Bipolar disorder not otherwise specified
Mood disorder due to a medical condition
Substance induced mood disorder
Mood disorder not otherwise specified

Each of these disorders may involve a depressive episode, manic episode, mixed episode, hypomanic episode or a combination of any two different episodes. Thus a Bipolar I disorder is characterized by one or more manic or mixed episodes usually accompanied by a depressive episode while a Bipolar II disorder is characterized by one or more Major depressive episodes accompanied by at least one hypomanic episode.

Further classification could involve determining whether the cause is primary or secondary and from here the terms primary mania or secondary mania evolve [11]. One can differentiate mania based on the cause by dividing it into primary or idiopathic mania and secondary mania (where there is an identifiable cause.) This classification of primary and secondary mania was first suggested by Robins and Guze in 1972 [12] and improved by Klerman and Barret and later Krauthemmer in 1978 [13]. However the distinction of primary versus secondary disorders was first muted by Alistair Munro.

Initially secondary mania was described by Robins and Guze as mania occurring in patients who had no previous or concurrent psychiatric illness. Klermman and Barret later described it as an illness following past history of medical, traumatic or pharmacological complaints and use. Krauthemmer took the concept further to describe secondary mania as mania that can occur in association with organic dysfunction – medical and pharmacological toxic – in patients with no history of affective disorder. He was also the first to describe the clinical characteristics of secondary mania being different from primary mania where he noticed that patients of secondary mania were older with no family history of mania. The concept of secondary mania is that a patient can present with symptoms that are similar to the diagnostic criteria for primary mania but with an identifiable cause. In some cases the clinical characteristics are different. Thus HIV secondary mania became to be recognized as a disorder of HIV infective brain degeneration.

Secondary Mania of HIV/AIDS

Over the last 10 years research done in Africa and Uganda in particular has shown that mental health issues in HIV are not just psychological reactions to having the disease but rather a consequence of the HIV virus attacking brain tissue [2].

Dementia, major depression, psychosis, and mania are some of the mental health conditions that have been studied quite extensively by Ugandan researchers and have been shown to be different entities from the same conditions in HIV negative populations [2, 3, 14–19]. Mental health disorders in HIV/AIDS seem to be a sequalae of the neuropathogenesis of the virus itself which leads to presentations of some mental health conditions to be different between HIV positive and HIV negative groups.

In the case of mania this has led to the development of the term secondary mania of HIV/AIDS also referred to as HIV mania which was well described by Nakimuli-Mpungu et al. [18]. They described secondary mania of HIV/AIDS as a distinct syndrome with different clinical presentation from patients with primary mania without HIV and bipolar mania in HIV. This differing clinical presentation impacts on treatment modalities prognosis and in low resource settings investigations and as such clinicians need to be aware of this syndrome.

Etiology

In primary mania there have been various studies on the different aetiologies of mania. It should be noted that they are usually multifactorial and as such a biopsychosocial model is usually adopted to define the different causes of primary mania. The main theories of mania include increased neurotransmitter function especially dopamine and serotonin; genetics proved through family and twin studies and psychodynamic factors as described by Abraham, Lewin and Klein [20]. From the late 1970s Krauthemmer suggested organic causes of mania. He noted that drugs metabolic disturbances and infections were all associated with developing manic episodes. Since then a large number of organic substances have been associated with development of manic symptoms (see Table 19.2).

Pathogenesis

As is the case for many psychiatric conditions that are co morbid with HIV, the pathogenesis is not entirely understood. Five main theories have been postulated to determine how HIV causes mania in particular. These include the following:

i. Direct effects of the virus on the central nervous system.
ii. Opportunistic infections and the metabolic effects associated with them.
iii. Drugs used in the treatment of HIV/AIDS like HAART especially the non nucleoside reverse transcriptase inhibitor Efavirenz and steroids.
iv. Psychological challenges associated with having HIV/AIDS.
v. HIV associated neuro cognitive disorders (HAND) causing brain degenerations
vi. HIV associated CNS neoplasms.

Table 19.2 Causes of secondary mania

Drugs of abuse
Alcohol abuse
Amphetamine abuse
Cocaine abuse
Hallucinogen abuse
Opiate abuse
Collagen vascular disease
Systemic Lupus Erythematosus
Infectious disease
Neurosyphilis
Herpes Encephalitis
Influenza
St. Louis Encephalitis
HIV/AIDS
Endocrine disease
Hyperthyroidism
Hypothyroidism
Neurologic disease
Multiple Sclerosis
Huntington's Chorea
Wilson disease
Head trauma
Complex partial seizures
Cerebrovascular accidents
Migraine headache
Neoplasms (esp. diencephalic or third ventricle)
Medications
Neuropsychiatric
Monoamine oxidase inhibitors
Heterocyclic antidepressants, SSRI
Methylphenidate
Disulfiram
Levodopa
Cardiovascular
Captopril
Hydralazine
Endocrine
Bromocriptine
Steroids
Miscellaneous
Baclofen
Bromide
Procarbazine

(continued)

Table 19.2 (continued)

Yohimbine
Cimetidine
Isoniazid
Vitamin deficiency
Vitamin B12 deficiency
Folate deficiency
Niacin deficiency
Thiamine deficiency

Adopted from Mania secondary causes in family practice notebook, http://www.fpnotebook.com/psych/Bipolar/MnScndryCs.htm. Accessed 10/30/2014

Previous studies have tried to determine the pathogenesis of HIV-related mania. HIV preferentially affects sub cortical gray matter such as the caudate nuclei and cortical white matter, both of which are important in the regulation of mood, thus manic symptoms indicating CNS HIV infection. HIV-related mania may be caused by accumulation of intracellular free calcium, which has been implicated in the pathogenesis of bipolar disorder [21] and has similarly been shown to be increased in HIV infected neurones [22, 23]. On the other hand, El-Mallakh suggested that mania or hypomania appeared to be related to immunosuppression and progression of HIV disease.

Clinical Features

Making a diagnosis of mania ideally entails following the set criteria as laid out in the DSM IV TR. In summary the classification states that the symptoms should last for at least 1 week (or less if hospitalization is required); should not involve a mixed episode, not be due to the effects of a substance and should affect social occupational functioning.

A patient with HIV mania usually meets the criteria set out for a manic episode. Primary mania is highly hereditary but in the case of HIV mania the patient usually does not have previous history of this illness or family history of the disease [16–19]. Patients with secondary mania of HIV/AIDS however present with irritability more than euphoria; are more over talkative with decreased need for sleep. They are more cognitively impaired with more perceptual disturbances [16–18, 24]. The DSM classification of a manic episode does not report any cognitive or perceptual disturbances.

In cases of primary mania or bipolar mania the patient will usually be in the late teens or early 1920s and usually has prior depressive episodes or manic episodes and family history suggestive of a mental illness. The clinical features of secondary

mania are distinct especially in terms of demographic characteristics [25]. Patients of secondary mania of HIV/AIDS in Uganda were usually uneducated older females of poor socioeconomic status as described by Nakimuli-Mpungu et al. [18]. In Caucasian populations patients of HIV mania were found to be older gay males who were well educated and of good socioeconomic status. The main demographic characteristic was age which supports the theory that secondary mania was more prevalent in older populations. This implies that a first episode manic episode in HIV populations usually occurs with a later age of onset. This differs from the secondary mania after a brain lesion where there is no noted age differences between patients who developed mania after a brain lesion and those without a brain lesion but who had mania [26]. In high HIV endemic populations, it is prudent to suspect a first episode manic episode occurring in later ages to be due to HIV/AIDS making routine HIV screening mandatory in all late onset manias [2].

In earlier case presentations of HIV mania patients were noted to present with AIDS defining illnesses like HIV wasting syndrome. Current case presentations however describe patients presenting with stage II symptoms of the World Health Organization Staging characteristics of HIV/AIDS like oral candidiasis. Indeed the occurrence of late onset first episode mania may herald HIV infection in the absence of other symptoms.

Investigations

Investigations usually involve a work up for initiation of HAART since Secondary mania of HIV/AIDS has often been found to be associated with lower immune status [16, 18]. Nakimuli-Mpungu et al. [18] showed that a CD4 count of less than 350 was associated with HIV mania while Lyketsos et al. [27] noted that patients without previous family history or personal history of a manic disorder presented much later in the infection presumably when the immunity was low. In any patient suspected to have secondary mania of HIV/AIDS an HIV test to confirm the diagnosis and immune function tests by CD4 count are paramount. There is also need to rule out co-infections like syphilis and cryptococcal meningitis which can present with manic symptoms as well. There are no specific radiological investigations for HIV mania but they might show concurrent AIDS defining illnesses like toxoplasmosis or cryptococcal meningitis. Use of rating scales like the Young Mania Rating Scale is necessary to gauge severity and monitor response to treatment.

Treatment

Pharmacological treatment does not greatly differ between management of secondary mania of HIV/AIDS and primary mania. There is however need to watch for side effects since there is documented evidence of worse extra pyramidal side effects

in HIV especially when typical antipsychotics are used. Most studies show a better side effect profile when atypical antipsychotics like risperidone are used but this also depends on which antiretroviral is being used. A case series by Kelly et al. [20] showed worse side effects when risperidone was given specifically with the protease inhibitor ritinovar/idinavir. In our setting nucleoside and non nucleoside reverse transcriptase inhibitors are our first line drugs for HIV/AIDS so atypical antipsychotics are preferred in HIV mania. For prophylaxis of recurrences, Sodium valproate is the preferred mood stabilizer as it has less drug-drug interaction with HAART regimens and a safer blood level.

Prognosis

Time to recovery is shorter in secondary mania of HIV/AIDS than primary mania [28]. DSM gives a range time of 4 weeks to several months for a typical manic episode to resolve but in secondary mania the time is usually shorter. This quick recovery seems to be irrespective of whether or not the individual is on HAART [28]. There is however a high risk of relapse even when there is good adherence to the psychotropic drugs. This necessitates need for mood stabilizers usually sodium valproate, carbamazepine or lamotrigine. Lithium carbonate in this population is not preferred because of a narrow therapeutic window and associated renal toxicity especially in wasted HIV positive patients.

Case Report

LJ was a 33 year old male from one of the central districts in Uganda. He was a taxi driver and of the protestant Church of Uganda by faith. He was newly married to NJ and the couple had no children. He had never attended any form of formal education.

LJ presented to the outpatient Mental Health Clinic of Mulago National Referral Hospital with complaints of headache, confusion and over talkativeness over 1 day. He had also been complaining of easy irritability, decreased sleep and restlessness for the week prior to admission. He was brought in by his wife who reported two episodes of vomiting and confusion on the morning of admission. He was also more talkative than usual and got easily angered. He had been sleeping poorly in the week prior to admission characterized by terminal insomnia associated with pacing around the house. LJ reported complaints of headache which had been on for the last 3 months and which “could just not go away.” The headache was associated with occasional blurred vision. He also accepted that he had been having difficulty sleeping for the last 1 month and was irritable. He denied having hallucinations of any sort during this episode. He did not report feeling sad or decreased interest in activities of daily living and he had a good appetite. He had

no thoughts of feeling worthless or committing suicide for the 2 weeks prior to this onset of this episode.

LJ had been diagnosed HIV positive 4 months prior to this admission at which time his baseline CD4 count was ten cells per microlitre. He had been started on HAART of Truvada and Nevirapine 1 month after diagnosis of HIV. He reported good adherence to HAART which was confirmed by his wife. There was no history of trauma or seizures. He denied using alcohol or any other substances of abuse and he denied any history of mental illness in the family.

Past psychiatric history revealed that this was his second admission in a 4 month period. On the first episode, he had had similar symptomatology but including auditory and visual hallucinations. He had improved after a 10 day admission and discharged on a low dose of Haloperidol which he had been on since discharge and he was adherent to it too.

Family and social history revealed a marriage to one wife with no children between them. His wife was also seropositive for HIV and on cotrimoxazole prophylaxis. LJ had a child born out of this marriage who stayed with the mother and he did not know this girlfriend's or child's HIV serological status or their whereabouts. He had not worked on his job as a taxi driver for sometime due to illness.

Physical examination revealed a Glascow coma score (GCS) of 15/15 with pupils equal and reactive to light and accommodation. The neck was soft with a negative Kerning's sign. He had decreased hearing sensation but all the other cranial nerves were intact. He had normal muscle power tone and strength with no increased deep tendon reflexes and normal sensation.

His Mental Status Examination (MSE) revealed a young man who was restless and pacing. He was not wasted, not febrile, not anemic and had no oral thrush. His speech was loud but not pressured. His mood was irritable but without suicidal ideas. He was preoccupied with his headache, had no delusions and no perceptual disturbances. He was disoriented in time but not in place and person. He had poor concentration and attention but good insight. His memory and judgment were intact.

His current mental state was quite different in some aspects to his first presentation where he presented with physical signs of immunosuppression characterized by oral thrush, gross wasting and anemia. His speech then was loud, pressured and he was extremely irritable and aggressive. His thoughts at that time were many, grandiose and not connected. He had mood congruent auditory and visual hallucinations. He was disoriented in time place and person with poor memory, attention, concentration abstraction and judgment. His insight was also poor then.

A DSM IV-TR Multi axial diagnosis of HIV related manic psychosis with traits of antisocial behavior was recorded on axes I and II respectively. Axis III had medical conditions of primary CNS pathology of HIV opportunistic infections with Toxoplasmosis, Cryptococcus meningitis and Tuberculosis meningitis were highly suspected but laboratory investigations for them were negative. So, they were subsequently ruled out. On axis IV HIV disease was documented as a predisposing factor, precipitated by the low CD4 count. LJ being on HAART with good social support from the wife were thought to be protective factors. His global assessment of function was 45 % on that first admission. Then more biological investigations

revealed slightly raised alanine transferase. A complete blood count was unremarkable with negative serology for syphilis, serum CRAG and toxoplasmosis titers. His CD4 count was 168 cells. Neuroimaging with a brain Computer Topography Scan was unremarkable. Psychological assessment involved using the Yang Mania Rating Scale while social investigations sought to trace the child and former girlfriend in order to determine their HIV serological status.

His management involved admission into the inpatient psychiatric ward with immediate treatment to contain the high agitation using 10 mg of IM Haloperidol and 50 mg of IM promethazine as initial doses. Once less irritable he was started on oral antipsychotic medication while on the ward of haloperidol 10 mg twice a day, benzhexol 2 mg twice a day and clonazepam 2 mg at night. He was also advised to continue with HAART and cotrimoxazole 960 mg once a day.

LJ soon improved in his mental state on this management and was discharged after 1 week of hospitalization. He was discharged on oral haloperidol 5 mg at night and oral benzhexol 2 mg at night. Plans were made to start him on the prophylactic mood stabilizer, sodium valproate.

Discussion

The above case shows the salient features of secondary mania of HIV/AIDS. This is a syndrome that is different from primary mania described in DSM IV TR especially in demographic characteristics, clinical features, treatment, course and prognosis. According to Nakimuli-Mpungu et al. [18], patients with HIV mania are usually older, uneducated and of poor social economic status. This is different to Caucasian western populations where patients with HIV mania are usually educated males of good socioeconomic status [27, 29, 30]. Secondary mania of HIV/AIDS is associated with a lower immune status and patients usually present later in the infection [18, 27]. LJ's CD4 count of 10 cells/ul supports the theory that in low resource settings a first manic episode in HIV/AIDS is suggestive of a low CD4 count and may as well be an indication to start HAART. Patients with secondary mania of HIV/AIDS present with irritability more than euphoria and are over talkative with decreased need for sleep. They are also more cognitively impaired and have more perceptual disturbances like hallucinations than patients with primary mania [18, 19]. This case illustrated these features.

Pharmacological treatment does not greatly differ between management of secondary mania of HIV/AIDS and primary mania. There is however need to watch for side effects since there is documented evidence of worse extra pyramidal side effects in HIV especially when typical antipsychotics are used. The high risk of relapse may also necessitate initiating mood stabilizing medication. In the HIV positive population, sodium valproate is the preferred mood stabilizer as Lithium carbonate has a narrow therapeutic window and associated renal toxicity.

Finally, remission of symptoms is faster in patients with HIV secondary mania with an average time of 2 weeks for remission. This quick recovery seems to be irrespective of whether the individual is on HAART or not [2].

Conclusion

This case report depicts an HIV-positive patient with manic symptoms that are not dissimilar in presentation to DSM IV TR criteria for a manic episode. His clinical picture is very typical of the clinical presentation of secondary mania of HIV/AIDS as described in the literature [16, 18]. It supports the theory that secondary mania of HIV/AIDS is a clinically distinct syndrome and represents infective brain degeneration. This is not unusual in African settings.

References

1. Centers for Disease Control and Prevention. Guidelines for laboratory test result reporting of human immunodeficiency virus type 1 ribonucleic acid determination: recommendations from a CDC working group. MMWR. 2001;50(20).
2. Musisi S, Kinyanda E, editors. Psychiatric problems of HIV/AIDS and their management in Africa. Kampala: Fountain Publishers; 2009.
3. Maling S, Todd J, Van der Paal L, Grosskurth H, Kinyanda E. HIV-1 seroprevalence and risk factors for HIV infection among first-time psychiatric admissions in Uganda. AIDS Care: Psychological and Socio-medical Aspects of AIDS/HIV, 2011;23(2).
4. Collins PY, Holman AR, Freeman MC, Patel V. What is the relevance of mental health in HIV/AIDS care and treatment programs in developing countries? A systematic review. AIDS. 2006;20:1571–82.
5. Lundberg P, Johansson E, Okello E, Allebeck P, Thorson A. Sexual risk behaviours and sexual abuse in persons with severe mental illness in Uganda: a qualitative study. PLoS One. 2012;7(1):e29748.
6. Musisi S, Wagner GJ, Ghosh-Dastidar B, Nakasujja N, et al. Depression and sexual risk behavior among clients about to start HIV antiretroviral therapy in Uganda. Int J STD & AIDS. 2013. doi:10.1177/0956462413495186.
7. Kraepelin. Manic Depressive Insanity and Paranoia. Kraepelin, Emi Journal of Nervous & Mental Disease. 1921;53(4):350.
8. Perris 1966. The distinction between bipolar and unipolar affective disorders C Perris - Handbook of affective disorders. London: Churchill: 1982.
9. Sadock BJ, Sadock VA. Kaplan & Sadock's concise textbook of clinical psychiatry. Philadelphia: Lippincott Williams & Wilkins; 2008. p. 205.
10. American Psychological Association. Diagnostic and statistical manual of mental disorders. Text Revised. 4th ed. American Psychiatric Association. 2000.
11. Krauthammer C, Klerman GL. Secondary manic syndromes associated with antecedent physical illness or drugs. Arch Gen Psychiatry. 1978;35(11):1333–9.
12. Robins E, Guze SB. Classification of affective disorders – the primary secondary, the endogenous reactive and the neurotic-psychotic. In: Williams TA, Katz MM, Shield JA, editors. Recent advances in the psychobiology of the depressive illnesses. Washington, DC: US Government Printing Office; 1972.

13. Klerman GL, Barrett JE. Clinical and epidemiological aspects of affective disorders. In: Gershon S, Shopshin B, editors. Lithium: its role in psychiatric research and treatment. New York: Plenum Press; 1973.
14. Akena DH, Musisi S, Kinyanda E. A comparison of the clinical features of depression in HIV-positive and HIV-negative patients in Uganda. AIDS Care. 2011; 23(2):171–8. Afr J Psychiatry. 2010;13(1):43–51.
15. Wong MH, Robertson K, Nakasujja N, Skolasky R, Musisi S, Katabira E, McArthur JC, Ronald A, Sacktor N. Frequency of and risk factors for HIV dementia in an HIV clinic in sub-Saharan Africa. Neurology. 2007;68:350.
16. Nakimuli-Mpungu E, Musisi S, Mpungu SK, Katabira E. Primary mania versus HIV-related secondary mania in Uganda. Am J Psychiatry. 2006;163:1349–54.
17. Robinson RG. Primary mania versus secondary mania of HIV/AIDS in Uganda. Am J Psychiatry. 2006;163:1309–11.
18. Nakimuli-Mpungu E, Musisi S, Mpungu SK, Katabira E. Early-onset versus late-onset HIV-related secondary mania in Uganda. Psychosomatics. 2008;49:530.
19. Nakimuli-Mpungu E, Musisi S, Mpungu SK, Katabira E. Clinical presentation of bipolar mania in HIV-positive patients in Uganda. Psychosomatics. 2009;50:325.
20. Kelly DV, Béïque LC, Bowmer MI. Extrapyramidal symptoms with ritonavir/indinavir plus risperidone. Ann Pharmacother. 2002;36(5):827–30.
21. Dubovsky SL, Christiano J, Daniell LC, Franks RD, Murphy J, Adler L, Baker N, et al. Increased platelet intracellular calcium concentration in patients with bipolar affective disorders. Arch Gen Psychiatry. 1989;46:632–8.
22. Linde PR, Zimbwa PS. A case of psychotic mood disorder in an AIDS patient. Cent Afr J Med. 1995;41:97–101.
23. Dreyer EB, Kaiser PK, Offermann JT, Lepton SA. HIV-1 coat protein neurotoxicity prevented by calcium channel antagonists. Science. 1990;248:364–7.
24. Cruess DG, Evans DL, Repetto MJ, Gettes D, Douglas SD, Petitto JM. Prevalence, diagnosis, and pharmacological treatment of mood disorders in HIV disease. Review article. Biol Psychiatry. 2003;54(3):307–16.
25. Evans DL, Byerly MJ, Greer RA. Secondary mania: diagnosis and treatment. J Clin Psychiatry. 1995;56 Suppl 3:31–7.
26. Starkstein SE, Pearlson GD, Boston J, Robinson RG. Mania after brain injury. A controlled study of causative factors. Arch Neurol. 1987;44(10):1069–73.
27. Lyketsos CG, Hanson AL, Fishman M, Rosenblatt A, McHugh PR, Treisman GJ. Manic syndrome early and late in the course of HIV. Am J Psychiatry. 1993;150:326–7.
28. Nakimuli-Mpungu E, Mutamba B, Nshemerirwe S, Kiwuwa M, Musisi S. Effect of HIV infection on time to recovery from an acute manic episode. HIV/AIDS (Auckl). 2010;2:1850.
29 . Kieburtz K, Zettelmaier AE, Ketonen L, Tuite M, Caine ED. Manic syndrome in AIDS. Am J Psychiatry. 1991;148:1068–70.
30. Ellen SR, Judd FK, Mijch AM, Cockram A. Secondary mania in patients with HIV infection. Aust N Z J Psychiatry. 1999;3:353–60.

Chapter 20
Case Presentation of Epilepsy Secondary to Cerebral Malaria

Harriet Nakuya

Abstract Epilepsy is the most common neurological disease in Uganda in both children and adults with a the prevalence of 2–5/1,000 of the general population and as high as 70 % in onchocerciasis volvulus affected populations. The causes are multiple but in the Ugandan and other African settings, the most common causes are usually infections in childhood (cerebral malaria, HIV etc.), birth trauma, brain injury in adulthood and substance abuse. Cerebral malaria, characterised by high fever, convulsions and /or coma is one of the deadliest forms of malaria and is caused by the Plasmodium falciparum malaria haemoparasite.

Epilepsy is a common sequel of cerebral malaria in highly endemic areas as is the case in most sub-Saharan African regions and it occurs mostly in children. It is postulated that red blood cells infected with malaria parasites sequestrate and clog brain capillaries which appear as petechial haemorrhages in the brain causing brain hypoxia and edema leading to convulsions and coma. Children with cerebral malaria are at risk of developing several adverse neurological outcomes including epilepsy, disruptive behaviour disorders (e.g. ADHD) and disabilities characterised by motor, sensory or language and learning deficits. These affect approximately 10 % of survivors of cerebral malaria and represent a form of injury to the brain or brain degeneration pointing. Epilepsy is highly stigmatised in Africa pointing to a need to educate the people and increase public awareness about epilepsy facts to demystify the disease so that the sufferers are not treated as outcasts and not to be stigmatized. This is in addition to malaria eradication programs.

Keywords Cerebral malaria • Epilepsy • Convulsions • Coma • Brain damage • Stigma • Prevention

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S. Musisi, S. Jacobson (eds.), *Brain Degeneration and Dementia in Sub-Saharan Africa*, DOI 10.1007/978-1-4939-2456-1_20

Abbreviations

HIV	Human Immunodeficiency Virus
MHC	Mental Health Clinic
SVD	Spontaneous Vertex Delivery
EEG	Electroencephalogram
RBS	Random Blood Sugar
WBC	White Blood Cells
FBC	Full Blood Count
FBS	Fasting Blood Sugar
Hb	Hemoglobin
CM	Cerebral Malaria

Introduction

Epilepsy is the most common neurological disease in Uganda in both children and adults as it affects individuals of all age groups. In Uganda the prevalence is 2–5/1,000 of the general population and as high as 70 % in onchocerciasis volvulus affected populations. The causes are multiple but in the Ugandan and other African settings, the most common causes are usually birth trauma, infections in childhood (cerebral malaria, HIV etc.), brain trauma in adulthood and substance abuse [1]. Cerebral malaria, characterised by high fever, convulsions and /or coma is one of the deadliest forms of malaria and is caused by the Plasmodium falciparum malaria hemoparasite. Epilepsy is a common sequel of cerebral malaria where there is a high prevalence of malaria as happens in Africa's malaria-endemic regions [1, 2].

Cerebral malaria is the most severe neurological complication of infection with Plasmodium falciparum. With >575,000 cases annually, children in sub-Saharan Africa are the most affected worldwide. Surviving patients have an increased risk of neurological and cognitive deficits, behavioral difficulties and epilepsy making cerebral malaria a leading cause of childhood neurodisability in the African sub-Saharan region [3]. The pathogenesis of the neurocognitive sequel is poorly understood: coma develops through multiple mechanisms and there may be several mechanisms of brain injury. It is unclear how an intravascular parasite causes such brain injury. However it is postulated that red blood cells infected with malaria parasites sequestrate and clog brain capillaries which appear as petechial haemorrhages in the brain causing brain hypoxia and edema leading to convulsions and coma. Understanding these mechanisms is important to develop appropriate neuroprotective interventions. This chapter examines the sequelae of brain injury in cerebral malaria, relating this to the pathogenesis of epilepsy as a long term outcome. The chapter explores prospects for improved neurocognitive interventions to reduce on this brain degeneration which is a leading cause of neuro-disability in sub-Saharan Africa [1, 4].

Cerebral malaria is a medical emergency demanding immediate diagnosis and treatment since it is highly fatal or often leads to long-term complications. This severe or complicated form of malaria affecting the brain, occurs predominantly in children, with a mortality rate of 15–25 %. It affects about one million children every year, primarily in sub-Saharan Africa. Coma, headaches, seizures and impaired consciousness are frequent manifestations of this infection. Children less than 5 years of age are particularly susceptible because of their low levels of immunity. It only takes one bite from an infected mosquito to contract the disease that directly affects the brain, causing fever, vomiting, chills, and coma [4, 5].

Although this type of malaria is most common in children living in sub-Saharan Africa, it should be considered in anybody with impaired consciousness that has recently travelled in a malaria-endemic area [6]. Cerebral malaria has few specific features, but there are differences in clinical presentation between African children and non-immune adults. Subsequent neurological impairments are also most common and severe in children.

The malaria parasite is usually found circulating in the blood stream causing fever, vomiting, chills and rigours. In severe cases, these parasites would go through the blood to the brain and the infected red blood cells sequester in the capillaries in the brain, and block these blood vessels, causing swelling of the brain (brain edema) [1, 2]. When this happens, the child may become unconscious, but a number of them recover to full consciousness. Also, other factors such as convulsions, acidosis and/or hypoglycemia can impair consciousness. Cerebral malaria is highly fatal and can kill rapidly when with poor management, or it is not recognised early or when it involves a non-immune person who has not been in a malaria-endemic area.

Children with cerebral malaria are at risk of developing several adverse neurological outcomes indicating brain degeneration. These include epilepsy, disruptive behaviour disorders (e.g. ADHD) and disabilities characterised by motor, sensory or language deficits. These affect approximately 10 % of survivors of cerebral malaria and represent a form of injury to the brain or brain degeneration.

Treatment of Cerebral Malaria

Cerebral malaria is a medical emergency. Treatment is tripartite:

- Specific antimalarial therapy (I.V quinine, quinidine, artimesinine etc.)
- Management of coexistent malarial complications including seizures, fluid and electrolyte imbalances, hypoglycemia, hyperpyrexia etc.
- Treatment of associated super infections [2].

At best, initial management should be in an intensive care unit. Generalized seizures can be followed by rapid neurologic deterioration, so prompt treatment is required. Subclinical or non-convulsive seizures should be suspected in patients with persistent coma [3]. Convulsions can be prevented by controlling fever and through judicious use of prophylactic anticonvulsants [4, 5].

It is important to support the family of a child suffering from Cerebral Malaria (CM). Many lay people in Africa may feel that CM is caused by supernatural forces (witchcraft) and attend traditional healers and faith healers to the detriment of the affected child as death may soon ensue. The long-term outcome of cerebral malaria is the highly stigmatised epilepsy and the affected children are often treated as outcasts in their communities and even families. The usual management of epilepsy should thus be multidisciplinary involving not only psychiatrists or neurologists, but also psychologists, social workers, nurses, O.Ts, educationists and the community (village) health team. Below is an illustrative case of epilepsy which was caused by cerebral malaria.

Case Report

Presentation and History

NP was a 21 year old female hair dresser, Catholic and single who stopped school in senior three (Grade 10). At the age of 4 years, she developed convulsions associated with a febrile illness which were managed as cerebral malaria at Nsambya Missionary Hospital in Kampala, Uganda. Months later, she developed recurrent unprovoked seizures but which she treated with local herbs as she invoked witchcraft for having brought on this "unfortunate disease" to her which she did not like to call epilepsy for fear of stigma. Nine years ago, she was formally diagnosed with epilepsy, after she presented to the Mulago hospital's Mental Health Clinic, (MHC). NP's fits were usually preceded by a right sided headache which lasted for 10 min, lip smacking, blank starring, thereafter paralysis of the left lower limb followed by paralysis of the left upper limb, then dizziness and eventually generalized tonic-clonic convulsions with loss of consciousness.

NP reported associated but occasional tongue biting, no foam formation and she denied a history of fecal or urine incontinence. The rate of the fits was 4 per week. She reported history of multiple injuries especially on the forehead following the falls. No burns. She denied a history of smoking, alcohol or use of any other drugs. She had no history of head trauma. She did not have Sickle Cell Disease.

NP had never had a history of hearing voices, seeing things or smelling things which other people could not hear, see or smell prior to the fits or after gaining consciousness. On gaining consciousness, she often wandered away from home. She missed many of her school days and could not concentrate in class. This interfered with her school performance. She faced a lot of stigma and segregation from her peers where no one wanted to sit next to her or discuss with her which led her to attain poor grades at school. Eventually, she dropped out of school in Grade 10.

NP was born normally by Spontaneous Vaginal Delivery from Nsambya Missionary Hospital in Kampala, Uganda. Her mother reported that labor lasted for only 5 h and the baby cried immediately and there was no need for resuscitation of the baby. Initially, she had normal developmental milestones and was not sickly in

her childhood till when she had the cerebral malaria, developed epilepsy and everything in her life changed. She was educated up to Senior Secondary 3 (Grade 10), quit high school and went to hair dressing vocational training where she obtained a certificate in hairdressing. People often described her as being reserved. She lived with her mother and was single. She had had a boyfriend for 2 years but who left her after finding out that she had epilepsy. She had no family history of mental illness.

Examination Findings

On physical examination all findings and systems were normal. On Mental Status Examination, in appearance and behavior, she was a young lady in a good nutritional state and who was well kempt with no mannerisms and no scars on her body. Her speech was normal, logical and coherent. Her mood and affect were normal and euthymic. She had no suicidal or homicidal ideations. Her thoughts were well connected with no of flight of ideas or loosening of associations and no blockage. There were no delusions, no obsessions, no overvalued ideas and no thought insertion or withdrawal. She was preoccupied with the stigma of her epilepsy illness and she lamented on how it had interfered with her schooling and relationships as well as her future plans including getting a spouse. She also worried about its chronicity and incurability and hence poor prognosis. Perceptually, she had no hallucinations, no illusions, no derealization and no depersonalization. In her cognition, she was well oriented in time, place and person. Her memory, immediate and 5-min recall, as well as intermediate, short and long term memory were all intact. Her judgment for safety, social situations and abstraction were all intact. She had normal average intelligence and her attention and concentration were intact. She had insight into her illness and lamented the problems it had caused her.

Diagnosis

A DSM IV-TR multi-axial formulation was carried out. On AXIS I she had Complex partial seizures with generalization. On AXIS II, there was no overt personality disorder; but she was withdrawn, isolative, socially avoidant and with low self esteem and low confidence. On AXIS III, she had past Cerebral malaria which was also on AXIS IV as her predisposing factor to the epilepsy. Her perpetuating and precipitating factors were not being on any antiepileptic medications and beliefs in the supernatural as causing her epilepsy. However, she was protected by having had some education, having a hairdressing vocation and a supportive mother. On AXIS V, she scored 80 %. She was currently functioning well, had her hairdressing job, could be self supporting and had been able to keep a boyfriend for over 2 years although he had left.

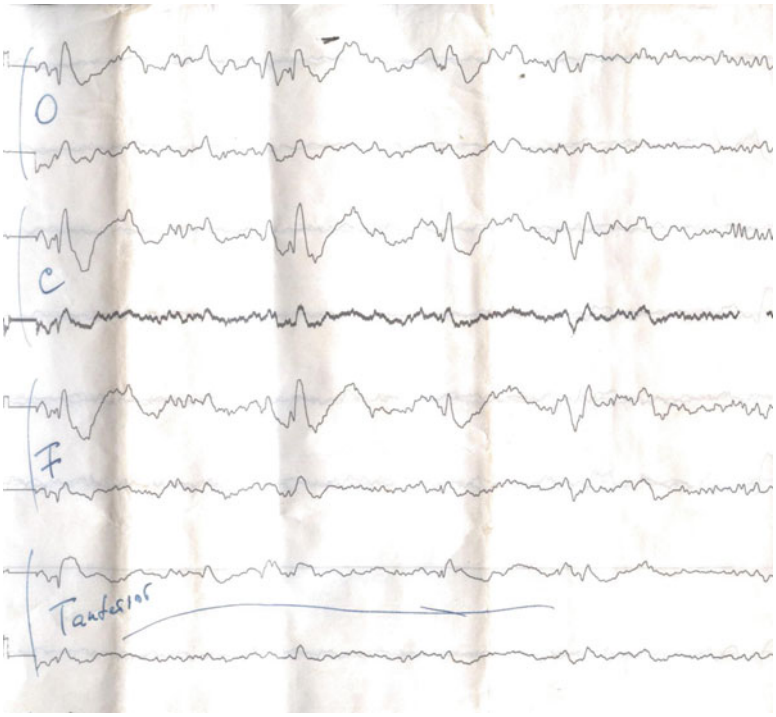

Fig. 20.1 EEG trace findings of NP

Investigations

The investigations carried out revealed normal CBC no haemoparasites, a FBS of 113 mg/dl, Hb electrophoresis-AS and her HIV and Syphilis serology were both negative. EEG findings showed mild diffuse slowing of activity and prominent paroxysmal abnormality consisting of slow waves and epileptiform discharges lasting from 2 up to 8 s in the left posterior temporal region (Fig. 20.1). The EEG diagnostic conclusion was Left Temporal Lobe epilepsy.

Treatment and Outcome

Before visiting the Mulago hospital MHC because her epilepsy illness, NP was being managed by traditional healers where she used to bath with herbs or take them orally. She had attributed what was happening to her to be witchcraft from her stepmother. At the Mulago hospital MHC, she was managed on carbamazepine and the frequency of her fits greatly reduced to only an occasional one once in a blue moon. She was initiated on carbamazepine and reviewed at monthly intervals as an outpatient.

NP and her family were psycho-educated about epilepsy, the fits, trigger factors, treatment and what to do with an aura. The epilepsy was demystified and its relationship to her childhood cerebral malaria was explained.

During her follow up on subsequent visits, she reported that the seizures had been adequately controlled to 2 fits a year. After 4 years on treatment, the carbamazepine dose was increased to better control the fits. Unfortunately, we could not do blood levels at Mulago hospital at the time. The patient was then followed up at 6 months intervals and she did well.

Discussion

This is a case of epilepsy secondary to cerebral malaria. The causes of epilepsy are multiple but the commonest in the sub-Saharan African setting are infections like malaria and onchocerciasis. This patient got convulsions in early childhood but later developed overt epilepsy as described above. The sequel of cerebral malaria may not be evident immediately after the infection but may occur years later. This patient she suffered the cerebral malaria at 4 years of age but the epilepsy developed at 9 years of age, 5 years later after the cerebral malaria.

When a child develops a chronic condition like epilepsy, their concentration and academic performance is often affected and many quit school as was this case. If they are still at school, many miss class. In this case, this was made worse by the fact that she used to be segregated at school and no one wanted to sit next to her in class, this is because in the African setting epilepsy is considered as a curse and the sufferers are often stigmatized and treated as outcasts in the community, even in their own homes.

There are several myths about epilepsy in the African setting. For example in Uganda there is a myth that the saliva of an epileptic is highly infectious. This translates into being avoided by others in fear of being infected. If an epileptic happens to get a fit even on a busy street, no one comes to his or her rescue due to such myths. In many African settings including Uganda, people have a tendency to seek alternative modes of treatment especially if diagnosed with chronic illnesses with no cure. This was seen in this patient who first sought treatment from traditional healers where she obtained herbs because the illness was attributed to witchcraft from the step mother.

In order to make a diagnosis of epilepsy, a high index of suscipicion is required as there are often no findings on examination or laboratory tests. In this patient the diagnosis was made basing on the history, In most Low and Middle Income Countries (LMIC) as are found in sub-Sahara Africa sophisticated investigations are not usually available, and in centers where they are available the cost is often prohibitive, forcing the clinician to rely on his/her clinical acumen. In epilepsy investigations, the EEG is informative in only 25–50 % of cases. The EEG confirmed the diagnosis in this patient. One also needs to carry out a series of investigations to look for any possible etiological factors responsible for the condition or at least to exclude them, e.g. HIV or Syphilis serology. Classifying the type of seizure is

useful in making the choice of drug for the patient. Thus focal seizures tend to do well on Carbamazepine or Sodium valproate. This patient responded well to Carbamazepine. Management is usually by psychiatrists and neurologists and is biological. However involving psychologists, social workers, nurses and mental health counselors is very important for the patient's and family's psycho-education and support.

Biological management involves use of various drugs selected depending on the seizure type and condition of the specific patient bearing in mind the drug interactions. A single drug at a low dose should be started with. If this is unable to control the fits, then the dose of the antiepileptic drug should be increased or consider adding another drug. This patient, she was started on a low dose of carbamazepine of 200 mg once a day, then to 400 mg nocte and lastly to 400 mg twice a day and the seizures were finally well controlled. There were no facilities to do serum carbamazepine levels.

Psychological management involved educating the patient about the disease, its trigger factors, aura and the need to comply with the treatment plus ways in which she could deal with the stigma associated with the illness. In this patient, the aura was the right sided headache and once experienced the patient stayed away from dangerous items like sharp instruments and fire to avoid being injured. However the trigger factor to her fits could not be identified.

Social management involves educating the care givers about the illness, teachers, and parents like it was done in this patient for support. For this patient, the mother was advised to keep her in school to get a vocation and she was able to attain a certificate in hairdressing thus enabling her to earn a living. The patient also neede social skills in how to be open and come out forthright in handling relationships when affected by a stigmatized condition.

Conclusion

Epilepsy in Africa is mainly due to infectious causes followed by trauma (birth injury, HIV, Syphilis etc.). These are all highly preventable and, therefore, point to the need to control them and manage them urgently and effectively in order to bring down the number of epileptic cases. This case illustrated brain degeneration from Cerebral Malaria, a disease wiped out in western countries, hence posing a challenge to Ugandans to also eradicate the malady. There is also need to educate the people and increase public awareness about epilepsy facts to demystify the disease so that the sufferers are not treated as outcasts and not to be stigmatized.

References

1. Labar DR, Harden C. Infection and inflammatory diseases. In: Engel Jr J, Pedley TA, editors. Epilepsy: a comprehensive textbook. Philadelphia: Lippincott–Raven; 1997. p. 2587–96.
2. Cegielski JP, Warrell DA. Cerebral malaria. In: Scheld WM, Whitley RJ, Durack DT, editors. Infections of the central nervous system. Philadelphia: Lippincott–Raven; 1997. p. 765–84.
3. Idro R, Jenkins NE, Newton CR. Pathogenesis, clinical features, and neurological outcome of cerebral malaria. Lancet Neurol. 2005;4(12):827–40.
4. Idro R, Kakooza-Mwesige A, Balyejjussa S, Mirembe G, Mugasha C, Tugumisirize J, Byarugaba J. Severe neurological sequelae and behaviour problems after cerebral malaria in Ugandan children. BMC Res Notes. 2010;3:104. doi:10.1186/1756-0500-3-104.
5. Idro R, Marsh K, John CC, Newton CR. Cerebral malaria: mechanisms of brain injury and strategies for improved neurocognitive outcome. Pediatr Res. 2010;68(4):267–74. doi:10.1203/00006450-201011001-00524.
6. Kvalsund MP, Birbeck GL. Epilepsy care challenges in developing countries. Curr Opin Neurol. 2012;25(2):179–86. doi:10.1097/WCO.0b013e328350baf8.

Part VI
The Burden and Care of Patients with Dementia in Sub-Saharan Africa

Chapter 21
Caring for the Elderly with Dementia in Africa

Seggane Musisi

Abstract Most of Africa's population is young. However, the fastest growing portion of Africa's population is that of those aged 60 years and above. Africa's older people suffer two common neuropsychiatric disorders namely Dementia and Depression in addition to numerous physical ailments. In the past, Africa's elderly were treated with much reverence and respect; and Africa's extended family system ensured their welfare whereby strong family bonds held together generations of the old, the matured, the youths and the children for the benefit of all. Today Africa is undergoing rapid demographic and socio-economic changes due to money economies, globalization, the migration of the young in search of jobs (brain drain, rural to urban migration etc.), and the HIV/AIDS epidemic. Growing old, in Africa today, translates into poverty, penury and anguish. There is no official social security system and pension schemes for the few are erratic. This, therefore, leaves the burden of care of the elderly, especially those with dementia, to the family/relatives with the actual caretakers being mostly women, often daughters or younger wives. These are the ones who carry the burden of care for the majority of the old and demented in Africa, a situation which has become increasingly unsustainable. The practice of putting the elderly away in nursing homes or homes for the aged is alien and repugnant to most African cultures and ways of life. There is thus a need to revisit the traditional African family support system and modify it to suite the modern changed lifestyles and realities of today's Africans and yet be in tune with the age-old African family system of caring for their old. The practical solution, for every African family with ageing frail parents, or grandparents, is to have a "granny apartment" and continue to care for their elderly including those with dementia and other infirmities. This way the African elderly will continue to live with their families in dignity till death and avoid the misery that, otherwise, awaits them in old age.

Keywords Old age • Dementia • Misery • Family • Burden of care • Granny apartment • Africa

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S. Musisi, S. Jacobson (eds.), *Brain Degeneration and Dementia in Sub-Saharan Africa*, DOI 10.1007/978-1-4939-2456-1_21

Aging in Sub-Saharan Africa

The elderly, also called Senior Citizens, have been variously defined in different countries, cultures and communities. Most western countries with long life expectancies consider a cut off of 65 years of age which denotes the retirement age in these countries as also being considered the age to be considered elderly. In developing countries, such as Uganda, most of the population is young and life expectancy is low. In Uganda, for example over 50 % of the population is below 15 years of age and life expectancy is, on the average, 51 years [1]. Thus, in developing countries the cut off age to be considered elderly is 60 years. Indeed, the WHO defines being elderly as either 60 or 65 years for a developing or developed country respectively. In this paper the elderly will be defined as 60 years and above.

Worldwide the population of the elderly is increasing at alarming rates [2]. This includes developing countries such as are found in Sub Saharan Africa including Uganda [3, 4]. For long, the emphasis on the demographic and health characteristics in sub-Saharan Africa has been on the high rates of fertility and on mortality from infectious diseases such as Malaria, Tuberculosis and HIV/AIDS and less on non-communicable diseases (NCDs) [3, 4], but this changing as the population of those over 60 years in increasing. The elderly suffer a proportionately higher burden of the NCDs be them physical or mental as well as a host of psychosocial problems. This, combined with the frailty of the elderly, their poor economic status, social isolation and deteriorating physical and mental health necessitates a need to care for them. This is a universal problem of increasing research interest. However, in Africa, there is very little in terms of research activities and data regarding old age especially in Sub Saharan African countries including Uganda. Yet whereas the ageing process in the developed world happened over a long period of time, that in Sub Saharan Africa, Uganda inclusive, is happening in a matter of a few decades [3, 4]. The attendant diseases of old age are therefore hardly addressed in Sub Saharan Africa. This includes the age-related brain degenerations, such as Dementia [3, 4].

Caring for the Elderly in Africa

Worldwide, people are living longer than ever before, a trend which has been taking place over many decades in developed countries but a relatively new phenomenon in developing countries but who have the largest numbers of people in the world. It is estimated that nearly 63 % of the population aged 60 and over are living in developing countries, and it is further projected that by 2050 nearly 1.5 billion older people will reside in developing countries [2]. These figures include Africa. This puts a huge demand on all systems of care and social services on the communities and governments of developing countries to care for their elderly folk [5]. In Uganda, the projected population of older persons today (2014) is estimated to be

Table 21.1 Population of persons ≥60 years in selected African countries, 2000–2025[a]

Country	Year 2000 population ≥60 years in thousands	Year 2025 population ≥60 years in thousands	% increase over 5 years in people ≥60 years	% increase of general population
Algeria	1,838	4,852	260	**140**
Kenya	1,260	2,166	170	**120**
Nigeria	5,599	10,944	200	**170**
CAR	180	261	150	**130**
South Africa	3,006	4,875	160	**80**

[a]Source: US Bureau of the Census International Database

1,540,000, indicating an overall growth rate of 40 % of people 60 years and above in a period of 10 years [1]. Today, the elderly constitute over 3.2 % of Uganda's population [6]. Such demographic shifts call for new research and legislative provisions to address this concern. Table 21.1 illustrates the demographic changes seen in some selected African countries regarding people aged 60 years and above [7].

In Africa, older people typically constitute the poorest groups of society. For example in Uganda according to the 'Uganda Reach The Aged Association', over 64 % of the older persons survived on less than one Dollar ($1) a day [19]. They did not have access to regular income and the majority did not benefit from social security provisions. The vast majority lived in rural areas where over 85 % of the active ones were engaged peasant subsistent farming. Many depended on one meal a day; others survived on one meal in two or more days, a situation that affected their health negatively [4, 8]. Various studies have found the elderly to often have many untreated health problems such as hypertension, stroke, diabetes, heart diseases, eye problems (trachoma and blindness), which diseases often lead to complications and permanent incapacitation [10]. Some of the most common mental health issues and concerns were depression, dementia, various psychoses, delirium and substance abuse (www.Agingcare.com). In Uganda, studies conducted at Mulago National Referral Hospital in Kampala reported similar findings with a reported 48 % prevalence of psychiatric morbidity among the elderly patients admitted on the non-psychiatric wards [12]. Depression and dementia were the most common mental health problems with a prevalence of 13 % and 8 % respectively [12].

Psychiatric services are poorly distributed in Africa, concentrating in urban areas and leaving many rural communities with no services [1]. Such services for the elderly are even more scarce. The vulnerability of the elderly in Uganda has increased especially over the last 30 years with elderly women bearing the brunt of it [1]. It is compounded by triad of "a culture which denies inheritance rights to women, the burden of HIV/AIDS orphans under their care and the absence of government run Social Security provision". Thus to be elderly and mentally ill in Africa, e.g. with dementia, is to live a life of misery, suffering and penury [1].

Traditionally, Africa had had established social networks that protected the elderly. These systems ensured strong bonds within the extended African family system consisting of multiple generations of the old, the grownups, the youths and the children [3]. These relationships provided for the needs of the old. The elderly were regarded with the utmost of respect as they were seen as the repository of knowledge and wisdom. However socio-demographic changes in Sub Saharan Africa have caused the elderly to be neglected resulting in much misery and penury with no economic security, no health care and no social supports [1]. The main causes of this problem has been the changed economic system (to a cash economy), massive rural-to-urban migration, the brain drain, relentless wars, political instability, the HIV/AIDS epidemic and the failure of Sub Saharan African governments to put in place and implement programs that address the needs, concerns and care of older persons [1]. This has thus left the burden of care for the elderly to relatives. With the African extended family system rapidly disintegrating, the demented elderly in Africa have suffered the most with these changed circumstances as they have become a burden to everyone. The HIV/AIDS epidemic has added more insult to injury by leaving the elderly to look after the many AIDS orphans whose parents have died [1]. There is also now a new sub-epidemic of the elderly HIV-positive individuals with significant HIV-associated neuro-cognitive disorders (HAND) which complicates the clinical picture and care of dementia in the African elderly [15]. Thus in summary, today the elderly in Africa are no longer playing the important role in society they used to. They are not acknowledged and the prevailing negative attitude towards them causes them much suffering, poor health, depressive disorders and somatic illnesses. The elderly are often segregated and marginalized leading to loneliness, loss of self-esteem and economic deprivation [3, 5–9, 11]. They are often abuse, exploited or their property stolen. Older women have even been abused sexually and physically, the latter following allegations of witchcraft practice and sorcery. A number of older persons have lost their lives, property or have been maimed in such circumstances [11].

Dementia in Africa

Dementia is defined as progressive global cognitive impairment, principally presenting as increasing forgetfulness and the problems which ensue hence from. The problem of dementia in Africa is increasing, especially with the increasing population of older people, the relentless HIV/AIDS epidemic which is now in its fourth decade and the increasing numbers of man-made accidents [1]. There are thus various causes of dementia in Sub-Saharan Africa. These include trauma, infections (especially HIV/AIDS), substance abuse (alcohol), CNS neoplasm, cardiovascular disease but most importantly for the old, the age-related brain degenerations. It is this last factor, the care for those suffering from the dementias of old age in Sub Saharan Africa, that this chapter will focus its concentration.

Gerontological Studies in Africa: The Case of Uganda

Studies addressing the elderly in Sub Saharan Africa are few and scattered, especially those addressing care burden. Najjumba-Mulindwa (2003) found that the elderly sick in Uganda lacked social support and care, always had feelings of negativity, frustration and powerlessness, were poor and often went hungry [11]. In a study of the elderly hospitalized on general hospital wards, Nakasujja et al. (2007 found a prevalence of depression at 13 % and dementia at 8 % [12]. The factors associated with the elderly's psychological distress were poverty, lack of social support and female gender [12].

Musisi et al. [16] in a Ugandan study of the elderly accessing psychiatric care at Mulago National Referral Hospital found the most common disorders to be Dementia at 46 % and Depression at 30 %. These were followed by alcoholism, bipolar disorder, anxiety disorder and psychotic disorder, with each being at about 6 % on average. Of these elderly psychiatric patients, the Male:Female ratio was 2:3, again showing that there were more elderly women than men. Their age range was 60–96 years (Mean = 74.1) with about half of them (49.1 %) being married. Of the married, the majority were men (77 %). Of the rest who were not married, the majority were widowed (40 %) with the biggest majority of this group being women (85 %). These figures suggested that among the elderly in Uganda, men remained married or remarried after losing their spouses but the elderly women remained unattached hence calling for care from others, mainly family. Only 6 % of the elderly were either divorced or separated and only 2 % were never married and these were Catholic nuns who lived in institutional care at their denominational mission stations. Thus in terms of care of these elderly, the majority of whom suffered either dementia or depression, the burden of care fell to the family with only 2 % being in institutional care. The question then was "Who, among the family members, actually looked after the elderly?" Table 21.2 shows the sources of care and support for the elderly psychiatric patients in Musisi's study [16].

As Table 21.2 shows, in that study, Musisi et al. (2008) found that the majority of the elderly, (58.9 %), were being looked after by their children especially daughters (32.3 %) who looked mostly after their ageing widowed mothers in about half

Table 21.2 Sources of care for elderly psychiatric patients

	Males (N = 22)	Females (N = 31)	Total (N = 53)
Source of support[a]	n (%)	n (%)	n (%)
Daughter	2 (9)	15 (48)	17 (32.3)
Son	6 (27)	8 (25.6)	14 (26.6)
Spouse	8 (36)	3 (9.6)	11 (20.9)
Self	4 (18)	4 (12.8)	8 (15.2)
Grandchildren	2 (9)	1 (3.2)	3 (5.7)
Others	1 (4.5)	1 (3.2)	2 (3.8)

[a]Some of the elderly had more than one source of support/care

(48 %) of the cases [16]. The sons looked after their ageing parents in 26.6 % of the cases and they did this in almost equal numbers (25.6 % mothers and 27 % fathers). Spouses looked after the elderly in 20.9 % of the times but this was mainly (younger) wives looking after their (elderly) husbands (36 %), meaning that men tended to remarry in old age but the widowed or separated/divorced elderly women remained unattached. About 15 % of these elderly looked after themselves with no one else to help and 6 % were found to be in extreme states of neglect with dementia, malnutrition and in very poor states of clothing, self-care and household environment. For these, only the neighbors paid cursory calls to them once in a while to give them food, water or do some house chores like laundry. The following case report illustrates this point.

Case Report I: Elderly Man with Dementia in Poor State of Care

GM was a 92 year old widowed elderly gentleman who lived alone in a rural area in his tin-roofed house with no piped water and no electricity (Fig. 21.1). He was a Retired Civil Servant. He had married two wives and had had 12 children. His first wife died of natural causes as a young elderly. He then lived with his second wife after retirement from the government job but she also died later on leaving him as a widowed elderly. He decided to live alone trusting his pension income and he would till the land for food. He had lost four of his children to HIV/AIDS and he helped look after some of the orphaned grandchildren. Three of his living children lived abroad in Europe and only rarely visited him when on vacations and only for a short time.

Fig. 21.1 Elderly and widowed GM with dementia in rural Uganda

The rest of his children were also grown up and lived in the city and only occasionally visited him in the countryside. His grand children had also grown up and had moved to the city looking for jobs. Most were unemployed and offered no help to GM.

GM did well for about 10 years after retirement at age 60. Then, he was still strong and healthy. Later on, his health began failing, beginning with his vision and he became functionally blind. He developed hypertension and often went into heart failure. He could no longer go to the city for his pension payments because it was too far and it became too expensive. His physical health waned and he could not till the land as strongly as before. His food production fell and he often went hungry. His memory then began failing and later developed frank dementia. He lost weight, developed malnutrition and anemia. He became quite frail and had no one to help him. Only the neighbors would pay courtesy calls to his house to give him food, water and do some of his laundry. Some delinquent youths on the village began stealing his farm foods and even items from his house. Some of his far stretched land was usurped by encroachers. There was no one to help. He fell into extreme poverty and neglect till some two grandchildren organized themselves on a rotating basis to visit him biweekly. Even then, this was not enough. GM needed continuous help on a daily basis.

HIV/AIDS, Dementia, and the Elderly

The Availability of Highly Active Anti-retroviral Therapy (HAART) has improved the lives of many people living with HIV/AIDS, thus enabling them to live longer lives. Moreover with the HIV/AIDS epidemic now in its fourth decade in Africa, many individuals infected with HIV in middle age are now of old age. These elderly living with HIV/AIDS are more likely to be vulnerable to the multiple social, psychological and physical problems associated with HV/AIDS including HIV-associated neuro-cognitive disorders or HAND with HIV-Associated Dementia (HAD) being the most problematic [18]. In a study of HIV immune-suppressed individuals at risk of cognitive impairment in Kampala, Uganda, Sacktor et al. (2009) reported that, in untreated HIV-infected individuals with advanced immune-suppression, HIV-associated dementia (HAD) was more common among patients infected with the subtype Clade D virus than among those infected with subtype Clade A virus [15]. These findings provided the first ever evidence demonstrating that HIV subtypes may have a pathogenetic factor in their capacity to cause cognitive impairment. With subtype Clade D being more common in Africa, this finding added further evidence of the risk of dementia neuro-pathogenesis among HIV-positive individuals in Africa, especially those who had had the infection for longer periods or in the more severely immune-suppressed as is likely to be the case in the elderly HIV-positives.

As regards to the care of the HIV Associated Dementia patients, Musisi et al. (2009) investigated the socio-demographics, clinical profiles and social supports of

Table 21.3 Socio-demographic characteristics of elderly HIV- positive patients in care, Kampala

Characteristic	Number (N = 118)	Percentage (%)
Sex		
Female	48	40.7
Male	70	59.3
Age (years)		
60–69	103	87
70–79	9	8
≥80	6	5
Marital status		
Married	44	37.3
Widowed	39	33.1
Separated/Divorced	10	8.5
Never Married	25	21.2
Occupation		
Employed/pension	23	19.5
Peasant Farmer	14	11.9
Self employment	22	18.6
Unemployed	59	48.9

HIV-positive elderly individuals in Uganda as seen at a specialized HIV care Centre in Kampala, Uganda using retrospective chart abstractions. Table 21.3 summarizes their demographic characteristics [17].

Among these elderly HIV-positives, the Male:Female ratio was 3:2 with 87 % being young elderly aged 60–69 years, 8 % were aged 70–79 years and 5 % 80 years and above. Over 37 % were married, 33 % widowed and 30 % unattached. About half of them (48.9 %) were unemployed and had no income with almost 30 % engaging subsistence self employment or peasant farming and only 20 with employment or pensions. Thus almost 80 % of the elderly HIV positives had no reliable source of income. Table 21.4 summaries their source of support.

Over a third (33.3 %) of these elderly HIV-positives said they were self-reliant and needed no support. However some 46 % felt they needed support but didn't get any. These latter lived in very poor conditions and were in most cases unattached as regards to their marital status (i.e. widowed, never married, divorced/separated). Family/relatives provided care/support in only about 20 % of cases and non-relative friends in 3.5 % of cases. Only 15 % of these elderly HIV-positives felt they had good enough support. None of the respondents were in institutional care.

In summary most of the elderly HIV-positives, who in most cases had HIV-associated neuro-cognitive disorders (HAND) including HIV-associated dementia (HAD) did not have care. They, in most cases, had to rely on themselves. Often they missed their appointments for follow up HIV care. A few lucky ones had a family member, usually their child, who looked after them. There was much secrecy regarding their illness of HIV/AIDS. The following case report illustrates these points.

Table 21.4 Sources of support and care of HIV-positive elderly with psychiatric illness

Support[a]	Number (N = 118)	Percentage (%)
Provided by		
Self-reliant	36	33.3
Family	19	17.7
Friends (non-relatives)	4	3.5
No support	49	46
Perceived quality of support		
Good	16	15
Fair	28	25
Poor	15	14
No support	49	46

[a]Some respondents had more than one source of support/care

Case Report II: Elderly Woman with HIV-Dementia Being Looked After by Her Children

WG was a 74 year old widowed HIV-positive lady. Her husband had died 15 years earlier from a long illness which the family, when in public, claimed to be cancer but which no one talked about. The family had lived in a war area and WG had been raped by soldiers, but this was kept as a family secret. Many years later, GW contracted Pulmonary Tuberculosis (PTB) which was successfully treated. Because of the doctor's suspicion, an HIV test was done and found to be positive. This was 10 years ago. WG was reluctant to tell her children of this diagnosis. It is when she lost a lot of weight as well as her hearing that she confided in her oldest daughter who worked in a hospital. She was then started on Anti-retroviral drugs (ARVs) which she took religiously. For over 5 years, WG developed progressive forgetfulness and would even lose her way home. She forgot where she had placed items including money, forgot her children's names and had been unable to take care of her Activities of Daily Living, ADLs. She also developed a seizure disorder. Her children were all grown up and busy with their families and jobs. WG had no one to look after her and she often missed her doctor's appointments and would forget to take her medications. On a psychiatric consultation, a diagnosis of HIV-Associated Neuro-cognitive Disorder (HAND) was made, more specifically HIV –Associated Dementia (HAD). The E.N.T consultant felt she had also developed central (nerve) hearing loss from the HIV involvement of the eighth cranial nerve given the virus's neurotropic propensity. Her seizure disorder was also part of her HAND.

Discussions regarding her care were held with her son and two daughters. Her son decided to convert two rooms of his "Servants Quarters" into a self contained "In-Law Apartment". He then moved his mother to permanently stay with his family who would look after all her needs including feeding, ADLs and taking her to hospital to attend for her HIV/AIDs care. GW is doing well, being looked after by her son and his family.

Conclusion

Africa is changing and changing very fast. Africa's population is young. However, the fastest growing portion of Africa's population is that of those aged 60 years and above. Studies in Africa's older people have shown them to suffer two common neuropsychiatric disorders namely Dementia and Depression [11–14, 16]. In the past, Africa's elderly were treated with much reverence and respect and considered the repository of wisdom; and Africa's extended family system ensured their welfare. Africans had established social networks that protected the aged, enhanced family support in situations of difficulty and provided strong bonds within the extended family system whereby generations of the old, the matured, the youths and the children all benefited [3, 4, 8, 11]. With the rapid demographic and socio-economic changes taking place in Africa today, the changed relations in a cash economy, globalization and the migration of Africa's young in search of jobs abroad (brain drain) or in cities (rural to urban migration), and the HIV/AIDS epidemic have all made it difficult for families to continue looking after their elderly as was the case before. Growing old, and especially very old, in Africa today translates into poverty, penury and anguish. Pension schemes are poorly administered and often not sufficiently indexed to inflation or cost of living. Indeed one soon learns not to trust in a pension. Moreover a number of government systems are run by corrupt officials who often make it difficult to receive one's pension money until a bribe is paid. There is no official social security. With the exception of religious missionary stations (usually Catholic missions), there is virtually no institutionalized care for the aged in most of Sub-Saharan Africa such as nursing homes or homes for the aged. This, therefore, lives the burden of care of the elderly, especially those with dementia, to the family/relatives. As well illustrated by the Ugandan studies, the actual caretakers in the families are usually women, often daughters or younger wives. These are the ones who carry the burden of care for the majority of the old and demented in Africa.

With the old African extended family system increasingly disappearing and in the absence of official social security, today's aged in Africa face a dilemma of existence. The question then of what should be done becomes imperative. The practical idea of putting the elderly away in nursing homes or homes for the aged is alien and repugnant to most African cultures, thinking and ways of life. Yet current governments in Africa do not have adequate pension programs, social security or health insurance to cater for the aged. There is thus a need to revisit the traditional African family support system and modify it to suite the modern changed lifestyles and realities of today's Africans and yet be in tune with the age old African family system of caring for their old. This new approach should be driven by the African belief that the aged are an important part of the family and community who play a very functional and valuable role in society. This is the traditional belief of Africans which should be cherished and enhanced to care for the aged and especially those with dementia in Africa. In this vein, I conclude by recommending that for every African household with ageing parents/grandparents, building "granny apartments" will help not only in the care of the elderly with dementia and other infirmities but also ensure family continuity. This is in addition to lobbying governments to estab-

lish community based support programs formulated by government policies for the specific social and health needs for the elderly. This way the elderly will continue to live with their families in dignity till death and avoid the misery that awaits them in old age where there are no such initiatives.

References

1. National Population Policy for Social Transformation and Sustainable Development. Population Secretariat, Ministry of Finance, Planning and Economic Development. Government of the Republic of Uganda. http://www.popsec.org. 2008.
2. UNFPA. World population prospects: the 2000 revision. New York: UN; 2001.
3. Nana Araba Apt. Ageing in Africa: revisiting traditional safety nets. Centre for Social Policy Studies University of Ghana, Legon. http://www.geocities.com/csps_ghana/ageing/safety.html. 2009.
4. Njuki C Reflections on ageing in Africa. http://www.globalaging.org/rural_aging/world/reflections.htm. 2001.
5. Nikolai B. Older persons in countries with economies in transition. In: Population ageing. challenges for policies and programs in developed and developing countries. UNFPA and CBGS; 1999.
6. Ministry of Health Report. Reducing poverty through promoting people's health: National Health Policy II. Kampala: Government of Uganda. www.health.90.ug/national_health. 2009.
7. Proceeds of the IPA eleventh international congress; Aug 17–22 2003; Chicago, USA. Quoting Washington, DC: US Bureau of the Census International Database; 2003. www.census.gov world population.
8. Ageing in Africa: the youngest continent. World Bauh Africa Report 2013. http://www.stpt.usf.edu/~jsokolov/africabb.htm.
9. UNAIDS and WHO. AIDS epidemic update. World Bauh Africa Report 2013. http://www.thebody.com/unaids/update/notes.html. 2000.
10. Dzuka J, Dalbert C. Well-being as a psychological indicator of health in old age: a research agenda. Stud Psychol. 2000;42(1–2):61–70.
11. Najjumba-Mulindwa I. Chronic poverty among the elderly in Uganda: perceptions, experiences and policy issues. http://www.docs.mak.ac.ug/sites/default/files/chronicpoverty/mulindwapdf. 2003.
12. Nakasujja N, Musisi S, Walugembe J, et al. Psychiatric disorders among the elderly on non-psychiatric wards in an African setting. Int J Psychogeriatr. 2007;19(4):691–704.
13. Baiyewu O, Bella AF, Adeyemi JD, et al. Health problems and socio-demographic findings in elderly Nigerians. Afr J Med Sci. 1997;26:13–7.
14. Ogunniyi A, Baiyewu O, Gureje O, et al. Morbidity pattern in a sample of elderly Nigerians resident in Idikan community, Ibadan. West Afr J Med. 2001;20(4):227–31.
15. Sacktor N, Nakasujja N, Musisi S, Katabira E, et al. HIV subtype D is associated with dementia compared with subtype A in immuno-suppressed individuals at risk of cognitive impairment in Kampala, Uganda. Clin Infect Dis. 2009;49(5):780–6. doi:10.1086/605284.
16. Musisi S, Nakasujja N, Katabira E. Diagnostic, psychosocial and care profiles of elderly patients attending psychiatric outpatients at Mulago Hospital, Uganda. Symposium on brain degenerations and emerging mental health challenges in Sub-Saharan Africa; 2012 Feb 1–3. Kampala: Golf Course Hotel; 2008.
17. Musisi S, Nakasujja N, Byakika-Kibwika P, Katabira E. Psycho-social and demographic profiles of elderly HIV-positive patients as seen at Mildmay Centre, Uganda. Proceeds of International Psychogeriatric Association annual conference; 2009 Aug 31–Sept 4. Montreal; 2009.
18. Sacktor N, Wong M, Nakasujja N, Musisi S, et al. Risk factors for HIV-dementia in sub-Saharan Africa. J Neurovirol. 2004;10:S3–83.
19. Uganda Reach the Aged Association. Advocacy and the older persons in Uganda. 2014. https://www.globalgiving.org/ptil/114/projdoc.doc. Accessed July 2014.

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S. Musisi, S. Jacobson (eds.), *Brain Degeneration and Dementia in Sub-Saharan Africa*, DOI 10.1007/978-1-4939-2456-1