NEUROLOGICAL MANIFESTATIONS AMONG CHILDREN INFECTED WITH HUMAN IMMUNODEFICIENY VIRUS/ACQUIRED IMMUNODEFICIENCY SYNDROME AND ASSOCIATED FACTORS

By

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A dissertation submitted in partial fulfillment of the requirements for the degree of Master of Medicine (Paediatrics and Child Health) of the University of Dar es Salaam

University of Dar es Salaam

November 2002



CERTIFICATION

The undersigned certifies that he has read and hereby recommend for acceptance by the University of Dar es Salaam a dissertation entitled: *Neurological Manifestations among Children infected with Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome and associated factors*, in partial fulfillment of the requirements for the degree of Master of Medicine (Paediatrics and Child Health)

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Acknowledgement

First of all I would like to express my sincere gratitude to my supervisor Dr K. Manji whose dedicated efforts, constructive criticisms and encouragement enabled the production of this dissertation. Many thanks to all my lecturers and other staff members in the department of paediatrics and child health for their contribution to this work.

Special appreciation to laboratory technicians Mr. C. Kagoma, Mr. J.Sufi and others for their hard work. Also to Mrs. K. Makata for her dedication and availability for HIV counseling. I am also thankful to Dr G. Kwesigabo and Mrs. R.Mpembeni for their statistical advice and assistance during analysis.

Thanks to Professor Earl Henderson of Temple University of United States of America, for encouragement and readiness to assist.

Sincere gratitude to my husband Dr Z. Kimambo, other family members and friends who prayed for me and supported me throughout the duration of my studies.

Most of all I give thanks to God for enabling me to complete this work.

Dedication

To Zabdiel my husband for your prayers, love, encouragement and support and to my daughter Joy.

ABSTRACT

Background

Human immunodeficiency virus (HIV) type-1 infection is a major cause of morbidity and mortality in children in Tanzania. Neurological manifestations are some of the commonest modes of clinical presentation of HIV/AIDS but they are underscored in Tanzanian children. To manage these children it is crucial to develop a better understanding of HIV-1 neurological manifestations and associated factors.

Objectives

To determine neurological manifestations, the factors associated with neurological manifestations in HIV-1 infected children, the association with the clinical stage of HIV, CD4 counts, age and nutritional status.

Methods

An unmatched case-control study was done at Muhimbili National Hospital in Dar-es-Salaam, Tanzania over a period of nine months. Children age one month to eight years admitted in the paediatric wards or attending follow-up at the outpatient clinics with clinical symptomatic HIV infection/AIDS or children known to have HIV-1 infection were enrolled into the study until the sample size of 190 patients was reached. Children were examined and investigated for

neurological manifestations and HIV status, CD4 counts and their nutritional status was assessed.

Results

From May 2001 – March 2002, a sample size of 190 patients was reached. Cases and controls were 107 and 83 respectively. Cases and control were comparable in terms of sex. Neurological manifestations found were mainly encephalopathy (91.5%), neuropathy (14.9%) and others accounted for (10.2%) of cases.

Global neurodevelopmental delay was present in 65% of cases. Locomotor development was the most affected parameter (75.7%).

Neurological manifestations were significantly associated with AIDS, moderate and severe stunting, (OR 4.44, 6.11 and 3.92 respectively).

There was no association between neurological manifestations and wasting or age. However in a separate analysis, encephalopathy was significantly associated with age, with a high peak age incidence being the second year of life.

In a sub-sample of 45 children, CD4 counts were done. There was no significant association between neurological manifestations and CD4 counts.

Conclusion

Encepahalopathy is the most common neurological problem; it is associated with age, with a high peak age incidence being in the second year of life.

Neurological manifestations are associated with AIDS, moderate and severe stunting.

Recommendations

HIV-1 infection should be suspected in children with neurodevelopmental delay even in isolated speech delay.

All HIV-1 infected children should have a thorough neurological examination and assessment.

Affordable means of reducing neurological manifestations in HIV-1 infected children need to be sought.

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ABBREVIATIONS

AIDS	Acquired human immunodeficiency syndrome
ARC	AIDS related complex
CDC	Center for infectious disease control
CMV	Cytomegalovirus
CNS	Central nervous system
CSF	Cerebral spinal fluid
EEG	Electroencephalography
EDTA	Ethyldiamine tetra acetic acid
ELISA	Enzyme linked immunosorbent assay
EMG	Electromyography
HAART	Highly active anti retroviral therapy
HIV	Human immunodeficiency virus
MNH	Muhimbili National Hospital
MRI	Magnetic resonance imaging
MUCHS	Muhimbili University College Of Health Sciences

OR	Odds ratio
PCR	Polymerase chain reaction
PML	Progressive multifocal leucoencephalopathy
QEEG	Quantitative electroencephalography
TNF	Tumour necrosis factor
UNAIDS	United Nations AIDS organization
WHO	World Health organizatio

INTRODUCTION AND REVIEW OF LITERATURE

1.0 Introduction

Human immunodeficiency virus (HIV) type-1 is a major cause of morbidity and mortality in children in Tanzania. Tanzania is one of the countries in the sub-Saharan Africa that is seriously affected by HIV. [1]

Most children are infected by vertical transmission from their mothers. Vertical transmission occurs prenataly across the placenta, intrapartum, or postpartum through breastfeeding.[2] According to the UNAIDS report on the global HIV/AIDS epidemic of June 2000, by the end of 1999; 1,300,000 children were HIV-infected worldwide, 1,000,000 of these children were in sub-Saharan Africa. Tanzania was estimated to have 59,000 children with HIV infection. It was further estimated that about 20,000-30,000 HIV-infected children died in 1999.[1] The prevalence of HIV type-1 infection in hospitalized children at Muhimbili National Hospital (MNH) in Dar es Salaam was found to be 19.2% in a study done in August 1995 to January 1996.[3] Another study done in 1988 among malnourished children at MNH showed a HIV-1 prevalence of 25%.[4] In 1989 the prevalence of HIV-1 infection in children with chronic diarrhoea at MNH was 39%.[5]

The annual report of MNH July 1999-June 2000, paediatric wards indicate that out of 9,453 children who were admitted, 413 (4.36%) were diagnosed and confirmed by laboratory results to have HIV-1 infection. These numbers do not include those who refused testing,

died before testing or were not tested before discharge, of those diagnosed to have HIV-1 61 (14.7%) died while in the ward.[6]

2.0 NEUROLOGICAL MANIFESTATIONS IN HIV-1 INFECTION

Neurological manifestations are some of the commonest modes of clinical presentation of HIV/AIDS. Neurological manifestations of HIV-1 infection are infrequently reported. HIV encephalopathy is infrequently diagnosed in children with delayed milestones and peripheral neuropathy is not being looked for, reported or managed at MNH.

2.1 Encephalopathy

Encephalopathy is a term used to describe a diffuse disorder of cerebral function that may be acute or chronic, progressive or static.[7]

2.1.1 HIV-1 Encephalopathy

HIV type-1 associated progressive encephalopathy is a common concomitant in the progression towards AIDS. Progressive encephalopathy is characterized by impaired brain growth, progressive motor dysfunction (increased tone and pathological deep tendon reflexes in younger children, ataxia or leg weakness in older children), cognitive impairment (loss or plateau of developmental milestones in younger children and, attentional deficits in older

children) and behavioural dysfunction (changes in personality, apathy, excessive irritability).[8,9]

Static encephalopathies represent fixed, nonprogressive neurologic or neurodevolopmental deficits in HIV type-1 infected children. Static encephalopathies may or may not be caused by HIV type-1 infection but are often associated with such identifiable insults as prematurity, in utero exposure to toxins or infectious agents.[8]

Piazza et al, [10] found that the incidence of central nervous system involvement by HIV-1 was 24% in infected patients and 37% in children with symptomatic HIV-1 infection. Neurological symptoms were observed in coincidence with worsening AIDS disease.

A study done on HIV infected children who were followed for a period of 7 years showed various neurological manifestations. The results showed that 33% of patients in stage B of the CDC classification (appendix 1) and 80% of patients with AIDS had neurological manifestations. Fifty percent (50%) of the patients with AIDS developed a sub acute progressive course or progressive plateau course and 30% a static course of encephalopathy.[11] Other studies found that 30%-60% of children with AIDS manifest a progressive encephalopathy.[12]

Pathological changes in electroencephalography (EEG) were seen in 54% of investigated patients with neurological deficits.[11]

Kwasa T.O,[13] noted that the prevalence of neurological manifestations in HIV infected patients at autopsy approaches 100%.

2.1.2 Neurodevelopmental abnormalities in HIV-1 infection

Neurological abnormalities occur frequently in children with symptomatic HIV infection and include cognitive, language and motor deficits as well as acquired microcephaly.[14]

Bovin et al, [15] studied 14 asymptomatic HIV-infected Zairian children (now Democratic Republic of Congo) under 2 years of age. They displayed social and motor developmental deficits on the Denver Developmental Screening Test. In a second study 11 children over 2 years of age had sequential motor and visual-spatial memory deficits on the Kaufman Assessment Battery for Children and motor development deficits on the early Childhood Screening Profiles. HIV-1 infection affects central nervous system structures mediating motor and spatial memory development, even in seemingly asymptomatic children. Piazza et al, [10] studied 88 children infected with HIV type-1. The mental development was examined using the Griffith scales. Fifty-five percent (55%) of the patients had serious developmental delay.

A study on neurodevelopmental outcomes in Ugandan children showed that more frequent mental developmental abnormalities were evident at various ages in HIV-1 infected children.[16] However in the same study, information-processing abilities, such as recognition memory, was spared from HIV-related deficits. They classified the courses into 2 broad categories; progressive (loss of previously

acquired language and cognitive skills) and plateau (failure to acquire additional developmental skills).

The development of neurocognitive impairment is associated with high levels of HIV-1 activity and the resultant severe degree of immunosuppression. Although many clinicians almost exclusively associate HIV-related cognitive dysfunction with HIV-1 encephalopathy and dementia, the aetiologies are numerous and include not only HIV infection affecting the brain, but also infections and neoplasms, as well as adverse effects of prescribed therapies.[17] Neurological abnormalities can be seen as early as the first 3 months of age and can precede signs of immune deficiency and symptomatic illness. Hypotonia, delayed or poor head control and decreased vocalizations are some of the early neurological manifestation of HIV-1 infection.[14]

2.2 Neuropathy in HIV

Neuropathy may complicate all stages of HIV infection. Different types of peripheral neuropathy have been reported associated with HIV infection.[18] Peripheral neuropathy in children is infrequently reported and underdiagnosed.[19] Peripheral nerve abnormalities are frequent in adult patients with HIV infection although their pathogenesis remains unclear.[20]. Neuropathies may complicate all stages of infection with HIV and may occur as early as 2-3 weeks after acute infection.[21] HIV type-1 associated neurological diseases occur as the

initial presenting clinical manifestation of acquired immunodeficiency syndrome (AIDS) in 3-7% of adult patients in contrast it was the initial presenting symptom in up to 18% in children and adolescents.[22] Neuropathy is one of the most common neurological manifestation of AIDS related complex (ARC) occurring in as many as 20% of patients.[21] Araujo et al, [23] studied 39 children with HIV-1, they found that 34% had symptoms and signs of peripheral nerve involvement. They also found a small trend (that was not statistically significant) of a higher prevalence for peripheral neuropathy occurring in children with encephalopathy and AIDS.

HIV-1 infection should be considered in almost any neuromuscular syndrome especially neuropathies with features of demylination.[24]

2.2.1 Types of neuropathy

Neuropathy is a pathological process affecting a peripheral nerve or a number of nerves. Mononeuropathy is a process affecting a single nerve. When multiple or several nerves may be affected it is called mononeuritis multiplex. Polyneuropathy is a diffuse symmetrical disease process usually progressing proximally. Its course may be acute, sub acute or chronic. Polyneuropathy may be motor, sensory, sensorimotor (mixed) or autonomic.[25]

2.2.2 Distal sensory or sensorimotor axonal neuropathy

Axonal degeneration occurs after a nerve has been sectioned or its axon is severely damaged. The axon and myelin sheath distal to the injury degenerate. Regeneration occurs with axonal growth down the nerve sheath and axonal sprouting from the stump. In 1997, Floeter et al, [19] found distal sensory and sensorimotor axonal neuropathy mostly in older aged children with HIV. Araujo et al, [23] studied children infected with HIV type-1 ranging from 5 years to 14 years of age, one third presented with distal sensory polyneuropathy. The presenting symptoms were pain mainly in the lower limbs, burning sensation in the lower limbs in some, and parasthesia in both upper and lower limbs. The symptoms although long lived did not interfere with daily activities and had a fluctuating course.

2.2.3 Demyelinated neuropathy

Demylination is damage to the myelin sheath of the nerve but the axon itself is preserved. This causes conduction block or marked slowing of neurotransmission.[25]

Acute or chronic inflammatory demylinating polyneuropathies may occur with otherwise asymptomatic HIV type-1 infection.[22] Demyelinated neuropathy is characterized by development of paresis of legs and arms. It develops over weeks and months. Acute demyelinating neuropathy may cause paresis in a matter of hours or days.[26]

In 1991, Raphael et al, [27] reported a case of a five year old boy with AIDS who developed an inflammatory demylinating polyneuropathy. In 1997, Floeter et al, [19] also reported of a HIV infected child with demylinating neuropathy.

Inflammatory demylinating polyneuropathies have good prognosis with neuropathy resolving spontaneously when treated with steroids or plasmapharesis.[22] This supports an immune component being involved in neuropathy.

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2.2.4 Median nerve compression at the carpel tunnel

Median nerve compression at the carpel tunnel is a mononeuropathy. Floeter et al, [19] reported 3 cases of HIV type-1 infected children with median nerve compression at the carpel tunnel.[19] Median nerve compression presents with tingling and pain in the hand. Sometimes in the forearm, followed by weakness of thenar muscles. Wasting of abductor pollicis brevis develop with sensory loss of the palm and radial three and a half fingers.[7]

2.2.5 Polyradiculopathy

Radiculopathy is a disease process affecting the nerve roots.[25] Polyradiculopathy is most likely of infectious aetiology. Cytomegalovirus (CMV) is a leading contender for infectious agents causing polyradiculopathy but herpes simplex and HIV are other possibilities.[21] Acute lumbosacral polyradiculopathy in AIDS is a

clinical syndrome with different aetiologies and variable clinical outcomes. Patients with lumbosacral polyradiculopathy reviewed by So.Y.T et al showed different clinical presentations. Patients with CMV radiculopathy developed a distinctive syndrome of rapidly progressive flaccid paraparesis and areflexia that was frequently associated with sphincter disturbances. A more benign syndrome was also identified. It that had a slower clinical progression and less severe neurological deficits than in patients with CMV radiculopathy.[28]

2.3 Pathogenesis of neuropathology in HIV-1 infection

Vertically transmitted HIV infection occurs in an immature developing fetus. The maturational stage of the nervous and immune system are critical in determining the outcome of HIV type-1 infection, when exposed to direct or indirect effects of the virus is likely to be of utmost importance. Innumerable dynamic interactions occur between these two systems during development and undoubtedly interact in complex ways with HIV variables.[29]

The mechanisms causing cerebral injury are poorly understood. Both direct and indirect host related pathogenetic mechanisms have been proposed.[8,30] There is little evidence that HIV type-1 damages neurons directly; rather, the damage appears to occur indirectly via viral proteins or neurotoxic factors causing excessive stimulation by excitatory amino acids such as glutamate and quinolate.[31] Indirect

effects of HIV infection in the brain have been proposed to be the most important pathogenetic factors.[30, 32, 33]

The only cells that seem to be directly infected by HIV type-1 are the microglia/monocyte and the giant cells derived from fusion of monocytes. It is hypothesized, therefore, that cortical neurons and white matter alterations in patients with this syndrome depend on the production of injurious soluble factors liberated by these cells and by astrocytes under the influence of many of these same factors.[34] In particular, certain viral proteins such as gp 120 and tat and cytokines produced by infected macrophages or activated microglia seem to induce neuronal dysfunction and finally loss of nerve cells.[30]

Although viral antigens can be detected in microglia and multinucleated cells in HIV type-1 encephalitis, most of the central nervous system effects of HIV type-1 infection cannot be attributed to detectable levels of viral antigen, suggesting that paediatric CNS is unusually susceptible to low levels of HIV type-1 infection.[35] However the direct involvement of HIV type-1 replication in neuronal cells has not been excluded. Early reports of HIV type-1 associated neuropathology described the presence of viral particles in some astrocytes implicating direct infection of the immature nervous system as a contributing factor to the observed neuropathology.

Autopsy of brain tissue from infants with encephalopathy detected HIV type-1 nucleic acids in astrocytes. The HIV-1 viral protein gp41

was detected only on macrophages and multinucleated giant cells; HIV-1 Nef protein was present in cells morphologically identified as astrocytes, further suggesting that HIV-1 establishes a persistent rather than a progressive infection in astrocytes.[36] Wiley et al, [37] found that brains of children with a progressive neurologic course showed readily detectable HIV antigen, while the plateau course showed readily detectable HIV-1. These findings suggest that in children with symptomatic HIV-1 infection, the progressive neurological deterioration is due to HIV induced damage followed by either limited penetration of virus into the central nervous system, or clearance of virus below detectable limits.[37]

2.3.1 Cerebral spinal fluid in HIV-1 infected children

Gallo et al, [38] detected several immunological markers in cerebralspinal fluid (CSF) of HIV-1 infected children. Intrathecal synthesis of immunoglobulins, free light chains IL-1 beta, IL-6 and M-CSF were demonstrated both in asymptomatic children and children with subacute encephalopathy. These findings further support the hypothesis that, an immunopathological subclinical process within the central nervous system may be early manifestation of AIDS. Cytokine detection in CSF may represent a useful diagnostic tool in evaluating the outcome of HIV-1 infected patients. Another study showed cytokines IL-1 beta and tumor necrosis factor alpha were increased in both CSF and serum of children with AIDS. [38]

Other studies in adults with peripheral neuropathy showed increased CSF protein levels and pleocytosis.[28, 39, 40, 41] Martinez et al detected antibodies against HIV-1 in CSF.[18]

Changes in CSF are therefore not specific for a particular neurological manifestation and are present even in asymptomatic children.

2.4 Other causes of neurological manifestations in HIV

Neurologic symptoms are common in HIV-infected individuals, and they result from a wide range of etiologic agents, including HIV itself and opportunistic pathogens.[42] Direct infection of the central nervous system was not appreciated in the early years of the AIDS epidemic. Neurological complications associated with AIDS were largely attributed to opportunistic infections. In 1985, several groups succeeded in isolating HIV-1 directly from brain tissue.[43]

Opportunistic CNS infections are uncommon in HIV type-1 infected children, limited predominantly to monilial and cytomegaloviral encephalitidies. Only a few cases of CNS toxoplasmosis, have been reported in children. CNS lymphomas often occur in the setting of systemic polymorphous, polyclonal B-cell proliferations that have been associated with Epstien-Barr virus infection.[34]

Progressive multifocal leucoencephalopathy (PML) is caused by Human Parpova virus. It presents with focal symptoms hemiparesis aphasia, visual loss, sensory loss and ataxia. Progressive multifocal

leucoencephalopathy has been described in HIV-infected children but remains rare.[26]

3.0 PROBABLE FACTORS ASSOCIATED TO HIV-1 NEUROLOGICAL MANIFESTATIONS

3.1 Nutrition

Malnutrition and cachexia are characteristic symptoms of HIV-1 infection and AIDS.[44] Malnutrition seen in HIV-1 infection is multifactorial and may occur as a constitutional sign of infection in the absence of overt clinical disease.[45] The weight loss results from low intake of food and selected nutrients as a result of anorexia and eating problems, impaired gastro-intestinal function and increased metabolic rate following secondary opportunistic infection or the HIV-infection itself.[46] There is some evidence that release of cytokines TNF alpha/cachectin into plasma or tissues may mediate weight loss.[45]

The relationships among nutritional status, infectious disease and the immune system suggest that nutrition may be a cofactor in human immunodeficiency virus progression. It has been demonstrated that poor nutritional status and infection affect the immune system and interact with each other.[47]

There is evidence that compromised nutritional and antioxidant status begin early in the course of HIV-1 infection and may contribute to disease progression.[48] Malnutrition increases with

disease progression and it strongly predicts survival independent of CD4 counts.[49]

Micronutrient deficiencies may contribute to the pathogenesis of HIV through increased oxidative stress and compromised immunity.[50] Micronutrient deficiencies have been associated with HIV-1 disease progression. Vitamins A and B12 deficiencies are associated with decline in CD4 cell count and low baseline status has been found to significantly predict accelerated HIV-1 disease progression.[51] Low plasma or serum levels of zinc, selenium and vitamins A, E, B6, B12 and C are common among HIV-1 infected populations.[52]

Vitamin B12 deficiency may result in a number of neurological and neuropsychiatric disorders. A study done to compare vitamin B12 levels and neurological, neuropsychological and mood state abnormalities in HIV-1 infected subjects did not indicate an important role for vitamin B12 in neurological disease of HIV-1 infection.[53]

Although the predominant cause of neurological and neuropsychological abnormalities appears to be related to HIV-1 infection of the CNS, other factors including malnutrition may also play a role.[54] Numerous environmental factors including nutritional status may confound the ability to discriminate between a primary or secondary role of HIV-1 infection in the various neurological problems of HIV-1 infection.[8]

3.2 CD4 counts and viral load in HIV-1 infection

Human immunodeficiency virus establishes latent infection in CD4 lymphocytes and macrophages. It can destroy CD4 cells by direct virus cytotoxicity, indirectly through the host cells, or by both means.[55]

The CD4 count and viral load are used as indicators of HIV-1 disease severity. High burdens of viral load are associated with increased immunosuppression and therefore low CD4 counts.

In the CDC classification system for HIV infection there are three CD4 T-cell categories namely (I) >500/L, (2) 200-499/L and (3) <200/L. The three categories represent normal levels of CD4 counts, moderate and severe immunosuppresion respectively. The CD4 counts are used as criteria to start antiretroviral therapy, PCP prophylaxis and monitoring of response to therapy.[56]

Current research suggests that infants with basal ganglia calcification and those with plummeting or low CD4+ counts are at particular risk of severe central nervous system disease progression.[57]

Childs et al, [58] found that CD4+ counts below 500 cells/mm^3 were predictive of HIV-1 associated dementia and sensory neuropathy in adults. High levels of systemic HIV-1 replication may drive the initiation of neurologic disease so effective suppression of HIV-1 may reduce the incidence of neuropathy.

3.3 Age

Older children and adolescents in contrast to infants and toddlers appear to demonstrate only subtle neurological dysfunction until very late in their illness. Neurological dysfunctions include attentional difficulties; fine motor tremors, visual sequencing problems and depressive effect.[57].

4.0 MANAGEMENT OF NEUROLOGICAL MANIFESTATIONS IN HIV

4.1. Management of HIV-1 encephalopathy

The pathogenesis of HIV encephalopathy is similar to that seen in acute neuronal injury and CNS degenerative diseases and may make HIV-1 encephalopathy amenable to pharmacotherapy. Prevalence of HIV-1 encephalopathy has not decreased despite the use of highly active antiretroviral therapy (HAART).[30] So far the use of specific HIV-1 antiretroviral treatment has shown limited effects on neurological manifestations in symptomatic children.[8]

Treatment with antiretroviral agents can at least improve neurologic functioning in some children with HIV-1 related encephalopathy.[14]

Funk et al, [11] found that zidovudine had a positive temporary effect ranging from 6-12 months in 54% of patients studied. Antiretroviral therapy has limited benefit if symptoms start in the second year of life.

Another study demonstrated significantly improved

neuropsychological functioning with continuous infusion zidovudine therapy. [59]

Combination therapy with zidovudine and didanosine has been found to be more effective than either of the two monotherapies against CNS manifestation. No long-term beneficial effect was indicated for zidovudine monotherapy compared to didanosine monotherapy.[60]

Protease inhibitors and combination antiretroviral therapy using reverse transcriptase inhibitors are being used increasingly in the treatment of children infected with HIV-1. Combination therapy not only significantly suppresses HIV-1 replication, but also lessens or even reverses some of the neurologic and neurodevelopmental sequelae.[62]

4.2 Management of HIV-1 neuropathy

Therapy is similar in both seronegative and seropositive patients with inflammatory demyelinating polyneuropatheis. Plasmapheresis is preferred to corticosteroids in seropositive patients as it is less likely to induce further immunosuppresion. Steroids should be used with caution.[24, 62]

So.Y.T et al, [28] found that adult patients with acute lumbosacral polyradiculopathy when treated with ganciclovir, led to clinical stabilization, although worsening during the first two weeks was common.

5.0 SPECIAL DIAGNOSTIC PROCEDURES

5.1 Magnetic reasonance imaging (MRI)/computed tomography scans (CT)

The MRI/CT scan are important in demonstrating changes in the brains of HIV infected children. Brain growth impairment is detected in children above 2 years of age in whom it cannot be detected clinically.

Cortical atrophy is seen with decreased brain weight for age. Subcortical white matter abnormalities and calcification of basal ganglia are also seen.

Some opportunistic infections can also be detected. Toxoplasmosis appears as contrast enhancing spherical lesions in basal ganglia or cortex which are surrounded by oedema.[62]

Progressive multifocal leucoencephalopathy (PML) appears as single/multiple lesions of white matter with no contrast enhancement or mass effect.[26]

5.2 Electroencephalography (EEG)

The electroencephalogram provides a continuous recording of electrical activity between reference electrodes placed on the scalp. Although the genesis of the electrical activity is not certain, it is likely to originate from postsynaptic potentials in dendrites of cortical neurons.

The EEG waves are classified according to their frequency as delta (1-3/sec.) theta (4-7/sec.) alpha (8-12/sec.) and beta (13-20/sec.) These waves are altered by many factors such as age, state of alertness, eye closure and disease states. Abnormalities of waveform include spikes and slow waves.[7]

Baldeweg et al, [63] did quantitative electroencephalographic (QEEG) investigations of patients with HIV type-1 infection to detect early signs of HIV brain involvement. Marked increase in background alpha amplitude preceded cognitive and neurological impairment in the symptomatic stage of infection. Elevation of alpha amplitude was also associated with changes in psychiatric status. Antiretroviral medication suppressed this alpha elevation, supporting the usefulness of QEEG in monitoring drug CNS effects. In context of clinical neuropathological and brain imaging data, it is suggested that these changes in alpha rhythm are the earliest, albeit nonspecific, signs of HIV brain involvement reflecting the predominantly subcortical prominence of the pathological process.

5.3 Nerve biopsy

The most commonly sampled nerve is the sural nerve, which is purely a sensory nerve that supplies a small area of skin on the lateral surface of the foot. Whole or fascicular biopsies can be taken. When the sural nerve is severed behind the lateral malleolus of the ankle,

regeneration of the nerve occurs in 90% of cases. The sural nerve is often involved in many neuropathies that are predominantly motor.[7]

Leger et al, [41] studied twenty-five patients with peripheral neuropathy, nerve biopsies in six cases showed axonal changes but surprisingly with marked segmental demyelination in two cases. Cell infiltration was also present in nerve samples in two cases. In another study on 13 adult patients with distal demyelinating polyneuropathy the nerve biopsy showed a mixed axonal demyelinating polyneuropathy with infiltration of mononuclear cells. Pzedborski et al, [40] found demyelination on sural nerve biopsy examination in patients with demyelinating polyneuropathy.

The nerve biopsy can be used to measure immune and viral replication involvement in the aetiology of peripheral nerve involvement in patients infected with HIV-1.

5.4 Nerve conduction velocity

Motor and sensory nerve conduction may be measured electrophysiologically by using surface electrodes. The conduction velocity in nerve fibers may be measured by stimulating a nerve at two points and finding the difference in the conduction time to onset of muscle action potential. If the distance between the two points is known, conduction velocity over this length can be calculated. Severe slowing of nerve conduction is characteristic of segmental demyelination.

Conduction velocity in sensory nerves can be measured by direct electrical stimulation of the nerve and recording nerve action potential at appropriate sites such as the wrist.[7] Martinez et al, [21] did electrophysiological studies in 22 patients with HIV-1 infection. The electrophysiological study had a higher diagnostic yield, 68% than clinical examination, 50% for peripheral neuropathy diagnosis.

5.5 Electromyography (EMG)

EMG is less useful in paediatrics than in adults. This is because of the technical difficulties in carrying out recording in young children and in part because the best results require patients cooperation for full relaxation and maximal contraction of a muscle. Most children are too frightened to provide such cooperation. EMG requires the insertion of a needle into the belly of a muscle and recording of the electric potentials in various states of contraction. Characteristic patterns distinguish degeneration from myopathic involment.[7]

6.0. RATIONALE

Neurological manifestations are common in children with HIV infection, yet are not actively looked for. Neurological manifestations are under reported and under recognized. To manage these children it is important to develop a better understanding of the effects of HIV-1 infection on the nervous system and factors related to development of neurological manifestations in HIV infection

The neurological manifestations can improve or resolve with treatment therefore the diagnosis of neurological disorders is crucial.

No study has been done at MNH on neurological manifestations of HIV-1 infection and factors related to HIV-1 neurological manifestations.

7.0 OBJECTIVES

7.1 Broad objectives

To determine neurological manifestations, the factors associated to neurological manifestations in HIV-1 infected children, the relationship to the clinical stage of HIV, CD4 counts, age and nutritional status.

7.2 Specific objectives: Were to determine: -

7.2.1 Neurological manifestations in HIV-1 infected children at Muhimbili National Hospital.

7.2.2 The association of neurological manifestations in HIV-1 infection to HIV clinical stage.

7.2.3 The association of neurological manifestations in HIV-1 infection to CD4 counts.

7.2.4 The association of neurological manifestations in HIV-1 infection to nutritional status.

7.2.5 The association of neurological manifestations in HIV-1 infection to age.

8.0 PATIENTS AND METHODS

8.1 Study setting

The study was conducted at the Muhimbili National Hospital (MNH), Dar es Salaam, Tanzania.

Dar es Salaam is the Tanzania's largest city. It's population has been estimated to be 3.6 million.[64] Children under five years of age are estimated to be about 20% of the population.[65]

Muhimbili National Hospital (MNH) is a tertiary referral and university teaching hospital in Tanzania. It has 199 pediatric beds and is divided into four main wards. General wards A and B, ward 17 a diarrhoea treatment unit and Makuti ward for severely malnourished children. From July 1999 to June 2000 a total of 9,453 children were admitted. The wards cater for all strata of people in Dar es Salaam as well as those referred from all parts of Tanzania.

Children were selected from the above mentioned wards and from out patient clinics.

8.2 Study design

An unmatched case control hospital based study design was used. The study was unmatched because age was an investigated factor. This does not affect the results since each age has a set of defined neurodevelopmental scores in standard assessment scales such as Griffiths mental developmental scales.

8.3 Sample size

The calculation for sample size has been done with the help of EPI INFO version 6.[66]

The ratio of controls/case is	1
Odds ratio worth detecting	3
%of exposure among controls [67]	8 %
The alpha risk is	5%
Power of the study is	80%

The percentage of exposure among controls being the percentage of children under five years of age with moderate and severe wasting malnutrition in sub Saharan Africa.

The calculated sample size was	210
Cases	105 patients
Controls	105 patients

Formula

$$\text{Sample size} = \frac{u\sqrt{[\pi_1(1-\pi_1) + \pi_2 (1 - \pi_2)]} + v \sqrt{[2\pi (1 - \pi)]^2}}{(\pi_2 - \pi_1)^2}$$

u one sided percentage point of the normal distribution corresponding to 100% minus the power. If the power of the study is 80% then u is equal to 0.84

v percentage point of the normal distribution corresponding to the significance level - 1.96%

π_1 proportion of controls exposed - 8%

π_2 proportion of cases exposed - 20.7%

π mean of π_1 and π_2

8.4 Study population

All children aged more than 1 month up to 8 years (inclusive) admitted in the mentioned paediatric wards were eligible for HIV screening if they were clinically identified to be moderately symptomatic for HIV (class B) according to CDC classification, or suspected to have paediatric AIDS according to WHO classification. Children who tested HIV positive were eligible for enrollment into the study as well as children who were admitted or attending the follow up out patient clinics and known to be HIV positive.

Informed written consent to participate in the study was sought from their parents or guardians. (see appendix 6)

All children had their history taken, a thorough clinical examination and investigations done. Those with neurological manifestations were identified.

Cases were children who were HIV positive with neurological manifestations.

Controls were children who were HIV-1 positive without neurological manifestations.

8.4.1 Exclusion criteria

- Children with known neurological disorders which are usually not associated with HIV-1 infection e.g., Downs syndrome and cerebral palsy.
- Children with known clinical metabolic disorders such as diabetes mellitus, hyperthyroidism and hypothyroidism.
- Children who were on HIV antiretroviral treatment.

8.5 METHODS

8.5.1 Recruitment

Recruitment was done daily from Monday to Friday except on public holidays. A maximum of 5 patients were recruited in a day. Eligible patients were selected from the mentioned wards and paediatric out patient clinics. Screening for HIV was done after pre-test counseling which was done by the principle researcher assisted by a nursing

officer trained to do HIV counseling. Those who tested positive for HIV-1 were recruited into the study.

8.5.2 Data collection

A structured questionnaire (see appendix 2) was used to obtain information from parents or caretaker and patient if 5 years old or more.

Information was obtained regarding HIV related symptoms and clinical conditions. The clinical conditions were diagnosed using characteristic clinical features, available standard investigations and were treated according to standard protocols.[68]

A history of developmental milestones was taken and was classified as normal, regressed or delayed.

Information regarding symptoms of weakness was asked and if the child was 5 years and above symptoms of pain, parasthesia and hypoesthesia were asked for.

A thorough clinical examination and anthropometric measurements weight, height, and occipital-frontal circumference were taken.

Blood pressure was checked in recumbent and standing positions in children who could stand (above 1 year). This was done to detect postural hypotension.

Neurological examination included higher functions and cranial nerves examination. Touch, pain and vibration senses were tested in older children.

A detailed developmental assessment was done using Griffith's mental developmental scales (Appendix 3). A modified Griffith's assessment was done by verbal information from the mother in children who were too sick to be assessed.

Investigations were performed for related factors. Cranial ultrasound was done in one patient and electroencephalography was done in one patient to aid diagnosis of neurological manifestations. Other special diagnostic procedures like CT scans, nerve conduction velocity and nerve biopsy could not be done. The CT scans could not be done because of financial cost involved where as the other investigations such as nerve conduction velocity cannot be done at MNH. This is a limitation of the study.

8.5.3 Case definitions

A patient was diagnosed to have encephalopathy if he/she had one or more of the following features; impairment of brain growth, decline of cognitive function and clinical neurologic dysfunction, (see Appendix 4 for definition of terms).

Diagnosis for peripheral neuropathy was made if the patient had one symptom and one sign described below.

Symptoms: distal pain, parasthesia, hypoaesthesia and weakness.

Signs; hypotonia, diminished tendon reflexes, hypoaesthesia and postural hypotension

8.6 Anthropometric measurements

8.6.1 Weight

Weight was taken using Seca scales to the nearest 100grams.

For children who could not stand, the weight of the parent/guardian was taken together with that of the child then the parents weight was measured separately and deducted to get the child's weight.

8.6.2 Height

Height was taken to the nearest millimeter using a height board/measure. For children who could not stand length was measured by a length board to the nearest millimeter.

8.6.3 Occipital frontal circumference (OFC)

The OFC was measured using a plastic tape measure to the nearest millimeter.

8.6.4 Interpretation and classification

Interpretation of OFC for age, weight for height and height for age was made using standard World Health Organization (WHO) charts. Classification of malnutrition, stunting (height for age) and wasting (weight for age) was made using the Waterloo classification (see appendix 5).

8.7 Investigations

8.7.1 Blood specimen collection

Blood was drawn from each child by femoral venepuncture using disposable syringes and needles. This was done after thorough cleaning of the site with a cotton swab soaked in 70% alcohol. About 5mls of blood was drawn and put into vacutainer EDTA bottles. The serum was separated for HIV-1 testing and cells were used for CD4 counts.

8.7.2 HIV testing

HIV-1 testing was done using enzyme linked immunosorbent assay (ELISA) for HIV.

8.7.3 CD4 counts

CD4 T-lymphocytes were quantitated using a fluocytometer at the department of microbiology and immunology. The CD4 counts were classified to indicate normal, moderate or severe immunosupression depending on age (see appendix 6). Due to financial constraints, the CD4 counts were done in only 45 children and these were analysed as a sub-sample. This is a limitation of the study.

8.8 Data processing and analysis

Data clearing, entry and processing was done using EPI-INFO version 6. Analysis was done using EPI-INFO version 6 and SPSS programmes.[66, 69]

The odds ratio was calculated as a measure of the strength of association between two variables, risk factor and neurological manifestations.

Bivariate analysis (cross tabulations) of risk factors against the outcome presence or absence of neurological manifestations was made. Each risk factor was treated individually and then collectively to all risk factors that showed significant difference in a multiple logistic linear regression analysis to assess the independent contribution of each of the confounding factors

8.9 Ethical issues

The parents were asked to give written informed consent. The consent form addressed all important concerns such as HIV testing, potential benefits, confidentiality, risks and rights of the patient.

Pre-test and post-test counseling was done by a trained counselor. Ethical clearance was sought from the Higher Degrees, Research and Publications Committee of MUCHS.

9.0 RESULTS

9.1 Patient Characteristics

During the study period (May 2001-March 2002) a total of 412 patients were recruited for HIV testing, of these 222 were HIV positive and 190 were HIV negative. The recruitment criteria for HIV testing was CDC class B and WHO classification. In this study the clinical criteria have a positive predictive value of approximately 55%.

Among the HIV positive group 32 patients were not included in the study because the children either died or were discharged from hospital before a neurological assessment could be done.

One hundred and ninety children were included in the study. There were 107 patients with neurological manifestations (cases) and 83 children without neurological manifestations (controls). There were 109 (57.4%) males and 81 (42.6%) were females. Among the children with neurological manifestations (cases) 65 (60.7%) were males and 42(39.3%) were females.

In the children without neurological manifestations (controls) 44 (53%) were males and 39 (47%) were females. The distribution of patients according to sex among cases and controls is shown in table 1. There was no statistical significance in distribution of cases and controls by sex (P=0.284882)

Table 1: Distribution of patients according to sex among cases and controls

Sex	Cases	Controls	
Male	65 (60.7)	44 (53)	109 (57.4)
Female	42 (39.3)	39 (47)	81 (42.6)
Total	107 (100)	83 (100)	190 (100)

$X^2 = 1.14$ P value = 0.284882

9.2 Neurological manifestations.

Table 2 shows the types of neurological manifestations among HIV-1 infected children (cases). The total number and percentage is more than 107 and 100% respectively. This is because some children had more than 1 manifestation. The most frequent type was encephalopathy 98 (91.5%). The other types were isolated speech delay (4), speech, eye and hand co-ordination delay (2), HIV encephalitis (1), CMV encephalitis (1), tremors (1), fasciculations (1) and afebrile seizures (1).

Table 2: Distribution of Neurological manifestations in cases

Neurological manifestations	Number n=107	Percentage
Encephalopathy	98	(91.6)
Neuropathy	16	(14.9)
Others	11	(10.3)
Total	125	(116.8)

Table 3: Distribution of Neurodevelopmental delay in cases

Developmental parameters		Number	Percentage
Locomotor	(n=107)	81	75.7
Personal social	(n=107)	45	50.5
Hearing and speech	(n=106)	55	61.3
Eye and hand co-ordination	(n=83)	36	50
Performance	(n=82)	45	64.5
Practical reasoning	(n=28)	14	50
General Quotients	(n=83)	28	65

Table 4: Mean Developmental Quotients in cases

	Age 1-30 mo		Age 31-96	
Locomotor	(69)	54.5%	(38)	67.0%
Personal social	(69)	65.6%	(38)	78.3%
Hearing and Speech	(69)	60.4%	(37)	72.1%
Eye and Hand Co-ordination	(52)	67.0%	(31)	70.4%
Performance	(52)	64.4%	(30)	68.7%
Practical reasoning	(2)	98.3%	(26)	76.9%
General	(52)	62.5%	(31)	72.8%

9.2.1 Neurodevelopmental delay

A neurodevelopmental assessment was done on recruited children using Griffith's neurodevelopmental assessment tool. Thirty children were not fully assessed because either they were too sick or afraid. In such children a modified verbal assessment was done by taking information from the caretaker. The modified assessment did not include eye and hand co-ordination, performance, practical reasoning and general quotient. Practical reasoning was done in children above 5 years who were able to co-operate. The denominator for the different developmental parameters varied according to the number of children assessed in a particular group. The distribution of

developmental delay in children with neurological manifestation is shown in table 3.

Locomotor delay was most frequent 81 (75.7%). The least affected parameters were personal social (50.5%), eye and hand co-ordination development (50%) respectively.

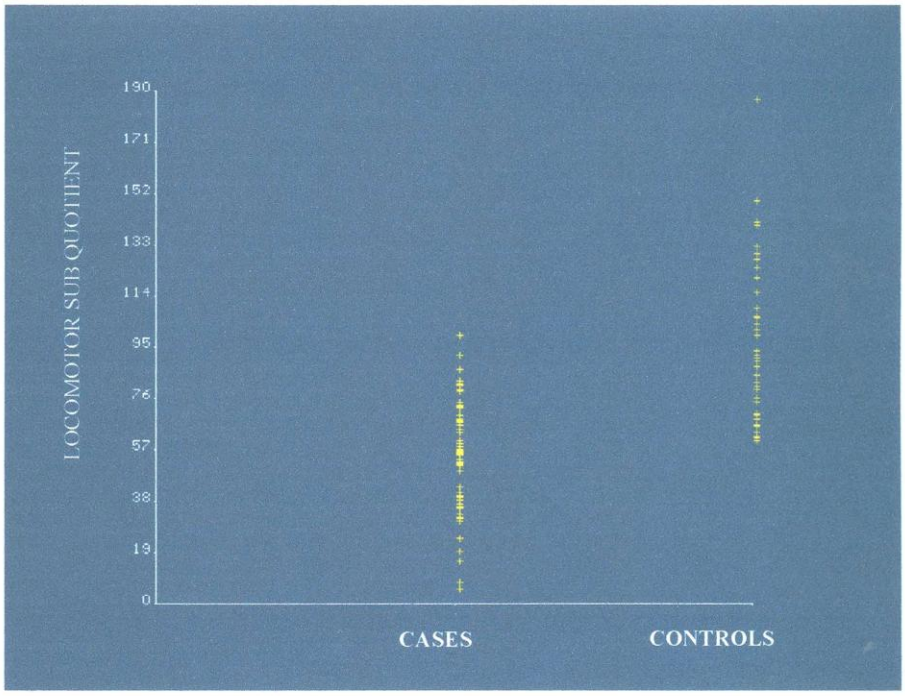
Table 4 shows the mean percentages of developmental quotients among children with neurological manifestations. In the age group 1-30 months a developmental sub quotient of 60% or more was considered normal. In this age group locomotor development is the only quotient with a mean percentage less than 60%. Among the categories, locomotor development was mostly affected both in the younger and in the older age groups 54.5% and 67% respectively.

In the younger age group hearing and speech development was next most affected (60.4%) whereas practical reasoning was not affected in this age group with a mean of 98.3%.

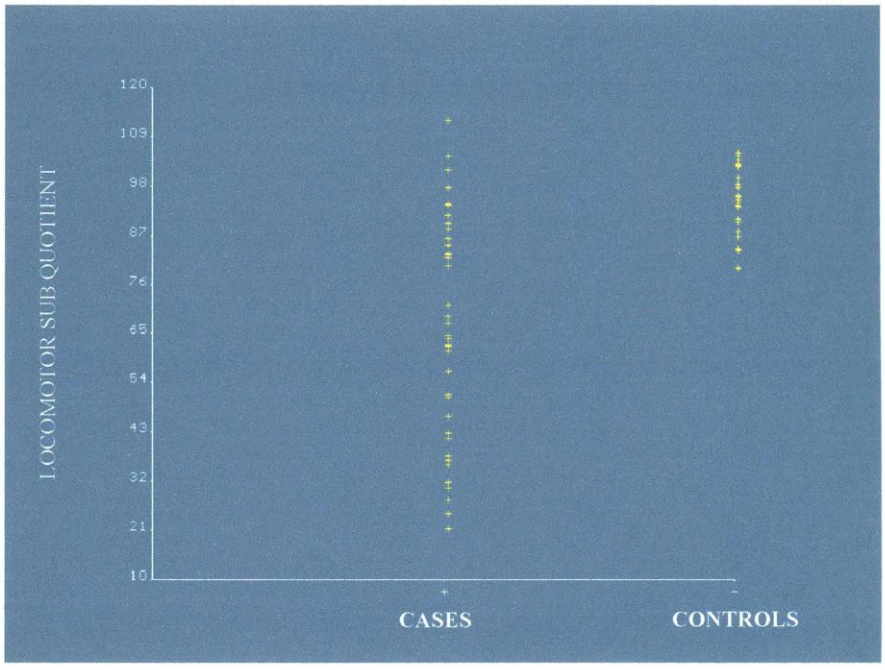
In the older age group performance was the next most affected (68.7%) whereas personal social (78.3%) and practical reasoning (76.9%)were the least affected.

Scatter diagrams

1: Locomotor development in HIV infected children aged 1-30months



2: Locomotor development in HIV infected children aged 31-96 months



Further analysis of locomotor development was done to show which age group was most affected. The scatter diagrams 1 and 2 compares locomotor development quotients among those with and without neurological manifestations in the age group 1-30 and 31-96 months respectively. In the younger age group of the cases (children with neurological manifestations) had scores more concentrated on the lower side with scores ranging from 6%-100%. In the older age group there were more variations with scores scattered between highest and lowest point of 21%-113% respectively. Therefore, locomotor development is more affected in the younger age group than in the older age group.

9.2.2 Neurological features

The neurological features are shown in table 5. The most frequent being delayed milestones 59 (55.1%) and microcephaly 57 (53%). Weakness and seizures were the least frequent 6 (5%) and 1 (0.9%) respectively. Parasthesia, (7.4%) was only present in 2 patients. It was asked for in children who were five years and above.

Table 5:Distribution of Neurological features in cases.

Neurological features	Number of patients n=107	Percentage
Impairment of brain growth *	57	53
Changes in neurobehavioral status	6	5.6
Diffuse symmetric hypotonia	15	12.4
Diffuse symmetric hypertonia	11	8
Increased tendon reflexes	15	14
Decreased tendon reflexes	16	14.9
Retardation of milestones	31	28.9
Delayed milestones	59	55.1
Parasthesia	2	7.4
Weakness	6	5
Seizures	1	0.9

(* Refer to appendix 4, page 86)

9.3 Distribution of neurological manifestations by age

The distribution of neurological manifestations by age is shown in table 6. The frequency of encephalopathy is highest in the second year of life (among the patients with encephalopathy). The frequency was 19.4% in the age group 13-18 months and 14.3% in the age group 19-24 months respectively. The peak age incidence for

encepalopathy is therefore in the second year of life. Neuropathy was more frequent in the second half of the first year (37.5%). Other neurological manifestations were more frequent in the same age group (45.4%), two out of five had isolated speech delay, 1 had speech as well as eye and hand co-ordination delay, 1 CMV encephalitis with chorea and 1 fasciculations.

Table 6:Distribution of Neurological manifestations in cases by age in months.

Age (months)	Encephalopathy	Neuropathy	Other	Total
1-6	7 (7.1)	1 (6.2)	0	8
7-12	13 (13.3)	6 (37.5)	5 (45.4)	24
13-18	19 (19.4)	3 (18.8)	1 (9.1)	23
19-24	14 (14.3)	0	1 (9.1)	15
25-36	22 (22.4)	2 (12.5)	0	24
37-48	8 (8.2)	0	0	8
49-60	5 (5.1)	2 (12.5)	3 (27.3)	10
61-96	10 (10.2)	2 (12.5)	1 (9.1)	13
Total	98	16	11	125

9.4 HIV-1 clinical stage

Table 7 shows the association between HIV-1 clinical stage and neurological manifestations. Ninety six (89.6%) of the children with neurological manifestations had AIDS. There was a strong association

between HIV-1 clinical stage and neurological manifestations. The difference was statistically significant (p=0.00007).

Table 7: Association between HIV-1 clinical stage and neurological manifestations

HIV-1 clinical stage	Cases n=107	Controls n=83	Total
AIDS	96 (89.7)	55 (66.3)	151 (79.5)
CDC STAGE B	11 (10.30)	28 (33.7)	39 (20.5)
Total	107 (100)	83 (100)	190 (100)
OR=4.44	X^2=15.76	p value= 0.00007	

Table 8:Association between CD4 counts and neurological manifestations

Degree of Immunusuppression	Cases n=107	Controls n=83	Total	OR	CI
Normal	8 (26.7)	5(33.3)	13 (28.9)		
Moderate immunosuppression	10 (33.3)	4(26.7)	14 (31.1)	1.56	(0.31, 7.82)
Severe immunosuppression	12 (40)	6(40.0)	18 (40.0)	1.25	(0.28, 5.53)
Total	30	15	45		

9.5 CD4 counts (refer to levels of classification appendix-6)

Table 8 shows the association between CD4 counts and neurological manifestations. The CD4 counts were done in a sub-sample of 45 patients due to financial constraint, 30 patients were cases and 15 patients were controls. The CD4 counts represent the different levels of immunosupression. Severe immunosuppression was present in 18 (40%) patients. There was no association between moderate and severe immunosupression and neurological manifestations. The odds ratios (OR) were 1.56 and 1.25 respectively. The X^2 was not statistically significant.

9.6 Nutritional status

Table 9 shows association between wasting malnutrition and neurological manifestations. The nutritional status was classified using the Waterloo classification. Wasting and stunting were classified using weight for height and height for age respectively. The two anthropometric measurements were assessed separately. Wasting was seen in 78.5% of the study population. Severe wasting was more frequent in patients with neurological manifestations (cases) as compared to those without (controls); (31.4%) versus (19.7%). Mild wasting was more frequent in controls, (33.3%) versus (21%) in cases. There was no association between mild, moderate and severe wasting to neurological manifestations. The odds ratios were

0.74, 1.38 and 1.87 respectively. The X^2 showed no statistical significance.

Table 9: Associations between wasting malnutrition and Neurological manifestations

Nutritional status	Cases n=107	Controls n=83	Total	OR	CI
Normal	21 (20.0)	19 (23.5)	40 (21.5)		
Mild wasting	22 (21.0)	27 (33.3)	49 (26.3)	0.74	(0.32, 1.70)
Moderate wasting	29 (27.6)	19 (23.5)	48 (25.8)	1.38	(0.59, 3.23)
Severe wasting	33 (31.4)	16 (19.7)	49 (26.3)	1.87	(0.79, 4.42)
Total	105 (100)	81 (100)	186 (100)		

Table 10 shows the association between stunting and neurological manifestations. Moderate stunting was more frequent in the patients with neurological manifestations as compared to those without; 37 (34.6%) versus 10 (12%). Among the patients without neurological manifestations 33 (39.8%) did not have stunting. There was a strong association between moderate and severe stunting to neurological manifestations. The odds ratios were 6.11 and 3.92 respectively. The chance of developing neurological manifestations is six times more for patients with moderate stunting and four times more for patients with severe stunting compared to patients without stunting.

Table 10: Association between stunting and neurological manifestations.

Nutritional status	Cases n=107	Controls n=83	Total	OR	CI
Normal	20 (18.7)	33 (39.8)	53 (27.9)		
Mild stunting	31 (29.0)	32 (38.6)	63 (33.2)	1.6	(0.76, 3.36
Moderate stunting	37 (34.6)	10 (12.0)	47 (24.7)	6.11	(2.5, 14.9)
Severe stunting	19 (17.7)	8 (9.6)	27 (14.2)	3.92	(1.45,10.6
Total	107 (100)	83 (100)	190 (100)		

9.7 Age

Table 11 shows the association between age and neurological manifestations. The percentages of patients with neurological manifestations are highest in the second and third year of life (18.7% 13,3% and 20.6%), whereas in the patients without neurological manifestations, the percentage is highest in the first year of life (15.7%) and (26.5%). There was no association between age and neurological manifestations and the difference is not statistically significant (p=0.0614).

Table 11: Association between neurological manifestations and age

Age (months)	Cases n=107	Controls n=83	Total
1-6	7 (6.5)	13 (15.7)	20 (10.5)
7-12	16 (14.9)	22 (26.5)	38 (20.0)
13-18	20 (18.7)	12 (14.5)	32 (16.8)
19-24	14 (13.1)	4 (4.8)	18 (9.5)
25-36	22 (20.6)	9 (10.8)	31 (16.3)
37-48	8 (7.5)	6 (7.2)	14 (7.4)
49-60	8 (7.5)	7 (8.4)	15 (7.9)
61-96	12 (11.2)	10 (12.1)	22 (11.6)
Total	107 (100)	83 (100)	190 (100)

$X^2 = 13.47$ P value =0.0614

Table 12 shows association between age and encephalopathy. The frequency of encephalopathy is highest in the second year of life, 19.4% were aged 13-18 months and 14.3% were aged 19-24 months. The frequency of patients without encephalopathy was highest in the first year, 14.1% were of age 1-6 months and 27.2% were of age 7-12 months. There was a significant association between age and encephalopathy (p value=0.006289).

Table 12: Association between encephalopathy and age

Age (months)	Encephalopathy n=98	No Encephalopathy n=92	Total
1-6	7 (7.1)	13 (14.1)	20 (10.5)
7-12	13 (13.3)	25 (27.2)	38 (20.0)
13-18	19 (19.4)	13 (14.1)	32 (16.8)
19-24	14 (14.3)	4 (4.4)	18 (9.5)
25-36	22 (22.4)	9 (9.8)	31 (16.3)
37-48	8 (8.2)	6 (6.5)	14 (7.4)
49-60	5 (5.1)	10 (10.9)	15 (7.9)
61-96	10 (10.2)	12 (13.0)	22 (11.6)
Total	98 (100)	92 (100)	190 (100)

X^2 =19.69 P value = 0.006289

Table 13: Multiple logistic linear regression

Variable	B coefficient	OR	p value
HIV clinical stage	-1.3709	0.2539	0.0020
Mild stunting	-1.1012	0.3325	0.0568
Moderate stunting	-1.1821	0.3066	0.0135
Severe stunting	-0.0842	0.9193	0.8559

Multiple logistic linear regression was done to assess the independent contribution of the two risk factors that showed significant difference (HIV-1 clincal stage and stunting). Even after controlling for other confounding factors, HIV-1 clinical stage and moderate stunting were still significantly associated with neurological manifestations. The p values were 0.002 and 0.0135 respectively. This is shown in Table 13.

10.0 DISCUSSION

This study involved children with symptomatic HIV-1 infection and those with full blown AIDS. The mode of transmission was thought to be perinatal in most children despite the fact that only few mothers had tested for HIV. One child was a haemphiliac who could have acquired the infection from contaminated blood. Though donated blood is screened for HIV by ELISA an unpublished report suggested that 1.5% of blood donors may be in the window period during the time of donation.[70] Therefore patients with recurrent blood transfusion are at greater risk of contracting HIV infection from contaminated blood. There was a history of sexual abuse in a 5 year old girl. Both patients did not have neurological manifestations.

The children in this present study were considered to have HIV infection after testing positive with double ELISA for HIV tests. Maternal antibodies against HIV-1 may persisit up to 18 months. However in a HIV prevalence study done at this center out of 235

patients who were below 18 months and were ELISA positive, 30 were p24 antigen negative. All 30 patients were less than 11 months of age. In this present study asymptomatic children were not included, 44 (23.1%) patients were below 11 months and 87 (45.8%) patients were below 18 months of age. Since children included in this study were symptomatic for HIV infection, it is likely that less would be negative by PCR testing. However lack of further testing to confirm HIV status is a limitation of this study.

The number of children with neurological manifestations (56.3%) was more than those without neurological manifestations (43.7%), thus accounting for fewer controls than cases. This is consistent with other studies that found the percentage of neurological manifestations among symptomatic HIV-1 infection to range between 40-70%.[30]

Among those with neurological manifestations, encephalopathy was the most frequent manifestation 98 (91.6%). Progressive encephalopathy was established clinically in 75 patients presenting with, regressed milestones, acquired microcephaly, pyramidal tract signs and spasticity. Static encephalopathy could not be proved since there was no long term follow up. Therefore, most encephalopathic patients (76.5%) had progressive encephalopathy. Funk et al [11] did a follow up study and found that among patients with encephalopathy, 50% had a progressive or progressive plateau course and 30% had static encephalopathy. Epstein et al [71]

described neurological manifestations in 36 HIV infected children, one out of three (33%) asymptomatic children, three out of twelve (25%) children with AIDS related complex, sixteen out of twenty one (76%) children with AIDS had progressive encephalopathy. Presence of encephalopathy correlated with poor outcome. Rigardetto et al [72] also reported a significantly higher mortality rate in patients with encephalopathy than patients without encephalopathy.

In the present study peripheral neuropathy was present in 14.9% of those with neurological manifestations. Twenty five percent of the children with neuropathy were 5 years and above. The diagnosis of neuropathy was difficult to make since most children could not express themselves. The lower incidence of neuropathy in this study could be related to under diagnosis as this study relied only on clinical information. It is known that electrophysiological studies have a higher diagnostic yield. Studies done on neuropathies have mostly been done in the developed world where facilities are available, this could account for the higher prevalences quoted.[19,23] There is no proper comparable group due to lack of data on HIV-1 related peripheral neuropathies in African children. Most studies reporting on neuropathies in children are in older children (5-18 years). [19, 23] This could account for the difference in prevalence and the pattern of clinical presentation. In the present study, 37.5% of children diagnosed to have neuropathy were in the second half of the first year of life. The most common symptoms were weakness,

hypotonia and reduced reflexes. Parasthesia was seen in only 2 patients who were 5 and 6 years of age respectively. None had pain or reduced vibration sense. The clinical findings suggest chronic inflammatory demyelinating neuropathy manifesting with weakness, hypotonia and reduced reflexes and distal sensory neuropathy presenting with parasthesia. Symptoms of autonomic neuropathy were not present in any of the patients studied. On the contrary, Araujo et al studied 39 children and found that the most common symptoms were, pain 13, parasthesia 15, reduced vibration sense 10 and reduced ankle jerks 11 patients.[23] Distal sensory neuropathy is the most common neuropathy in HIV infected adults and children.[19, 23, 62] However distal sensory neuropathy was found in older children.[19]

Neuropathy is also causally related to the use of anti retroviral drugs in children with HIV infection. In our study none of the children were on HAART and this perhaps could explain the lower rates of neuropathy in our study. Araujo et al [23] found neuropathy in one third of patients studied. They also found that, out of 13 patients with peripheral neuropathy 8 developed symptoms after use of potentially neurotoxic drugs.

Among the 16 patients with neuropathy in the present study, only 3 did not have encephalopathy. This is similar to findings by Araujo et al who found a higher prevalence of encephalopathy among patients with neuropathy though it was not statistically significant.[23]

In the present study, HIV encephalitis was diagnosed in a 20 months old male child who presented with loss of consciousness, hypertonia and increased reflexes for three weeks after which he died. The CSF protein was raised and microbiological examination revealed no bacterial growth.

Central nervous system opportunistic infections are uncommon in children, when they occur, they are mostly due to monilial and CMV encephalitides.[35] However, in this study central nervous system infections were much less than those reported in another study (0.9%) versus (33.8%).[73]

Only one patient was diagnosed to have an opportunistic central nervous system infection (CMV encephalopathy). This was an 8 month old male child with blindness, failure to thrive and chorea. Fundoscopy was suggestive of CMV retinitis and cranial ultrasound scan revealed periventricular calcifications. Another study found a higher prevalence of CMV infection than that found in the present study 6.8% versus 0.9% .[73] In the present study, all children were not screened for opportunistic infections and brain CT scans that could have shown features of CNS infections were not done. This could explain the differences seen.

In the present study, afebrile recurrent seizures were reported in a six-year-old boy whose mother died of AIDS. The seizures were generalized tonic clonic and he had no other problem. The EEG

revealed paroxysmal bursts of bilateral synchronous spike and wave complexes evoked by activation procedure. In two other studies done by Funk et al and Rotta et al abnormal EEG's were found in HIV infected patients even in the absence of seizures 54% and 45% respectively.[11, 73] Seizures are not a common neurological manifestation in HIV-1 infected children, however the frequency of seizures in the present study (0.9%) is much less than that quoted in other studies.[3, 73] Other studies have not specified whether or not the seizures were accompanied with fever or associated with infections. This could account for the difference seen. Rotta et al [73] found seizures in 6% of patients. A study done in the same setting as this study showed seizures were more common among non HIV infected than infected patients 9.8% and 3.1% respectively.[3]

Delayed developmental milestones was the most common symptom among patients with neurological manifestations 55 (59%). These findings are consistent with a study done by Piazza et al who also used Griffith's mental scales for neurodevelopmental assessment of children with HIV-1 infection. They found serious developmental delays in 55% of patients.[10] Neurodevelopmental delay in HIV-1 infected children has been reported in many studies in Africa and developed countries.[15, 16, 74, 75] Many of the studies quoted used other scales for developmental assessment therefore are not directly comparable. Smith et al,[76] further studied the effect of timing of HIV-1 infection on neurodevelopmental delay, they found that early

infection (HIV positive<48 hours after birth) was associated with lower Bailey motor scores from 4 months of age and lower mental scores from 12 months of age compared to late infection (>48 hours), whereby at 30 months, the motor and mental scores differed by 10 and 16 points respectively. The Bailey mental scores in the early HIV positive group declined 0.72 standard score per month, whereas the estimated average decline of the late HIV positive group was 0.30 per month.

The present study showed that among the neurodevelopmental parameters, locomotor delay was the most frequent among cases in both age groups (1-30 months) 54.5% and (31-96 months) 67% respectively. Chase et al [75] followed up HIV infected children up to 30 months of age. They found early (4-16 months) and persistent delay in locomotor development, deceleration in mental development occurred between 17-30 months.

In the present study, delay in performance as a measure of cognitive neurodevelopment was present mostly in the older age group. Personal social development and practical reasoning was least affected in the older age group. Where as practical reasoning was not affected in the younger age group. In a Ugandan study Drotar et al followed up perinatally HIV infected children for the first 24 months of life, and they found that cognitive development measured by puzzle performance using Bailey Mental scores was less powerfully affected as compared to motor development. They also

found that information processing abilities, such as recognition and memory were spared from HIV-related deficits.[16] Though assessment was done using a different mental scale from the present study, it shows that performance (puzzle performance in Bailey mental scores) and practical reasoning (information processing abilities, recognition and memory in Bailey mental scores) is spared in the younger age group. Therefore it is consistent with the findings in this study.

As seen in table 3, speech delay was present in 61.3% of patients with neurological problems making it second to motor delay. Tardieu et al [77] did cognitive assessment in school aged children and found speech and or language delay or articulation disorders in 44% of patients. The difference in ages of the children assessed may explain the difference seen.

In the present study four patients (3.7%) had isolated speech delay. These findings were consistent with another study, which reports a prevalence rate of 5%.[73] Coplan et al [78] studied early language development in children exposed to or infected with HIV. Among the 9 HIV infected infants studied, 7 manifested language deterioration on the mean language milestone scales. Five (55.5%) of these had a normal or near normal neurologic examination. In another study Wolters et al further studied language in HIV infected children using scales that test expressive and receptive language. They found that language scores declined significantly between 6-24 months. To

begin with, expressive language was more impaired up to 24 months. Then both expressive and receptive language declined significantly after the second year despite antiretroviral therapy.[79]

Microcephaly (53%) was the second most common sign, it was accompanied by developmental delay in 96.4% of patients. Microcephaly was detected in 17 children above two years suggesting that the insult to the brain began earlier on in infancy. If the insult begins after the second year of life, brain atrophy can only be detected by CT scan or MRI, which was not possible to do during this study. Rotta et al [73] found 75% of HIV infected patients had brain CT scan abnormalities.

In the present study most of the children studied were below five years of age (88.4%). There was no significant association between age and neurological manifestations. A separate analysis was done to find out the association between age and encephalopathy since it was the most common neurological manifestation. There was a significant association between encephalopathy and age (p value 0.006289). The frequency of encephalopathy was the highest in the second year of life. This is consistent with a study by Drotar et al who followed up vertically HIV infected infants from birth to 24 months and found abnormal neurological examination was found in 40% of cases at 6 months and 56% of cases at 18 months.[16]

In the present study eighteen patients (18.3%) below one year had encephalopathy. Rigardetto et al [72] found that encephalopathic patients in whom neurologic signs began in the first year of life, have a worse prognosis.

In this study most patients had growth failure; presenting as stunting (72%.) and wasting (78%). The findings in this study are similar to those seen in various studies done in African children infected with HIV.[79, 80, 81]

Studies that followed up HIV-1 infected children up to 2 years found that linear growth is affected from 3 months with stunting increasing at 6, 9,15 and 18 months.[80, 83] In a South African study, weight for length was significantly lower only at 9 months in the HIV infected compared to the HIV negative group. Weight for age was significantly lower at 3, 6 and 9 months. [80] In an American study there was no statistical significant difference in mean weight scores between the HIV infected and uninfected children. [83] This could be due to early use of anti-retroviral therapy and supportive nutrition in the developed world.

In this study wasting was not associated with neurological manifestations. This could be due to the wasting occurring within a short time. It is consistent with other studies. Araujo et al [23] found that presence of undernourishment was not associated with peripheral neuropathy. Brouwers et al [54] studied the role of

nutritional factors on neurobehavioral manifestations of symptomatic HIV-1 disease in children. Contrary to expectations, an increase in weight seemed to correlate with a decrease in neurocognitive function, however, the results were not statistically significant.

In the present study moderate and severe stunting was significantly associated with neurological manifestations with odds ratios of 6.11 and 3.92 respectively. This is consistent to findings by Pollack et al who found that neurodevelopmental delay was positively correlated with decline in linear growth. They studied linear growth and neurodevelopment, they found that postnatal linear growth in HIV infected children declined in the first 6 months of life whereas neurodevelopmental delays were noted at 12 months. They further studied the correlation of linear growth and development to HIV viral load. Both decline in linear growth and neurodevelopmental delay were also positively correlated to HIV viral load.[84]

Most of the patients studied had AIDS. This reflects the nature of children admitted at MNH paediatric wards. Muhimbili National Hospital is a tertiary centre therefore more children with chronic ill health are referred for further management. The strong association of AIDS with neurological manifestations is consistent with other studies.[10, 11]

There was no association between level of immunosuppression and neurological manifestations. This is in sharp contrast with other studies.[56, 57] These findings could be due to the small sample of patients and the number of cases that was twice that of controls among those tested for CD4 counts.

Since neurological manifestation correlated with clinical stage, stunting and (in the case of encephalopathy) to age but not with CD4 counts; it is speculated that HIV encephalopathy is directly related to viral load and may not be influenced by immunosuppression. It is known that HIV encephalopathy may occur even without significant immune suppression.

The clinical stage of HIV and moderate stunting, significantly associated with neurological manifestations in multiple logistic linear regression. However these two factors are closely related since patients with advanced disease are more likely to be stunted.

11.0 CONCLUSIONS

- Encephalopathy is the most common neurological problem in HIV-1 infected children being 91.6% of patients with neurological manifestations.
- The peak age incidence for encephalopathy is in the second year of life.

- There are various degrees of developmental delay in all age groups with the motor development being most affected.
- Neurological manifestation in HIV-1 infection were associated with AIDS, moderate and severe stunting.

12.0 RECOMMENDATIONS

- HIV-1 infection should be suspected in children with neurodevelopmental delay even in isolated speech delay.
- All HIV-1 infected children should have thorough neurological examination and neurodevelopmental assessment.
- Affordable means of reduction of neurological manifestations need to be sought.

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