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seizures were controlled with easily available and affordable anti-epileptic drugs. Cause of death in the dead patient was thought to be from cerebral edema. Other atypical presentations have been reported with PML. One is the occurrence of PML in patients with multiple sclerosis treated with Natalizumab who present more with cognitive and behavioural deficits[15].

The greatest limitation in this report is the absence of Polymerase Chain reaction in the center. Diagnosis of PML usually rests on the neuroimaging in the appropriate clinical context. This is further confirmed by CSF Polymerase chain reaction for the JC Virus DNA in an ideal situation. The availability of PCR will further enhance diagnosis in future studies.

CONCLUSION

PML is not a rare disease which is also seen in Africans especially in the setting of HIV disease. Clinicians in these areas need to have a high index of suspicion in HIV patients with neurocognitive deficits, focal neurological deficits and new onset seizures bearing in mind that PML may herald the HIV disease as the first manifestation. The availability of neuroimaging in the centers is a great boost and has made the diagnosis of PML easier.

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reported in HIV patients [5]. One study reported as much as 82% of PML cases seen in HIV positive persons[6]. The two cases of PML we described above were both HIV positive. PML is associated with both HIV-1 and HIV-11 and usually occurs in the setting of very poor immunological status as expressed by low CD4+ count (<200cells). The CD4+ count of the first patient was very low (19cells/uL). Unlike other HIV-associated opportunistic infections of the central nervous system, there have been reports of PML occurring in patients with high CD4+ count(>500cells) [7].

Within the HIV population, the epidemiology and prognosis of PML have undergone additional changes since the late 1990s. The incidence of PML has not changed much with the HAART era unlike other HIV-related opportunistic tumours and infections [8]. The introduction of HAART however transformed PML from an almost uniformly fatal and inexorably progressively disease to one in which long term survival is expected [8, 9]. One person has survived for more than 12 years [10]. Mortality therefore has decreased since HAART became the standard of care. Case fatality was 50% in our patients which is very high. This is probably because the dead patient was unable to commence HAART. The other patient on HAART was discharged and has done well.

The incidence of PML is known to be low in India and Africa due to diagnostic challenges and differences in JC virus isolates [11]. It is mainly due to this reason that few cases have been reported in Africa. Another possible explanation is that of the HIV and JC virus interactions [11] .There has been no previously reported cases of PML in our center. However, the recently purchased CT scan (though MRI is more sensitive) in the center made the diagnosis possible in these cases. This lends credibility to the fact that PML may have been under reported before now because of the dearth of diagnostic modalities. Further reports are therefore expected not just from our center but from other centers in Nigeria. There yet remains the challenge of the steep cost (for most of our patients) of the CT scan and the unavailability of Polymerase Chain Reaction (PCR) testing to isolate the JC virus in the diagnosis.

Consideration of PML in the differential diagnosis is based on the patient's susceptibility and the signs and symptoms of the disease. In an otherwise immunologically healthy individual, PML rarely accounts for focal neurological deficits [3]. What more, predisposed individuals are not always obvious for example, HIV-positive individuals who have not been diagnosed with HIV infection may present with PML as the heralding manifestation of their disease [12]. This was the case with our second patient who had no prior symptoms before the diagnosis of PML when she presented in status epilepticus. The HIV screening was done seven days earlier as part of the routine work up for an appendectomy. It can be said that PML was the first major manifestation of her disease.

The neuropathological evaluation reveals the multifocal nature of the disease, but its presentation is typically unifocal and MRI may demonstrate multifocal pathology [13]. Unlike other major opportunistic disorders that produce focal brain lesions (e.g. cerebral toxoplasmosis, primary CNS lymphoma), which characteristically progress over the course of hours or a few days, PML evolves over several weeks [13].However, PML demonstrates more rapid progression than AIDS dementia complex (ADC).

Focal neurological deficits are usually required to consider the possibility of PML. In recent times however, cognitive and behavioural abnormalities have been noted to be presenting features especially in individuals taking immune-modulating agents [12, 13]. Our first patient had focal neurological deficits while the second had no focal neurological deficits.

Seizures are not expected In PML since it is strictly considered a white matter disease. Seizures are generally a feature of cortical involvement of the lesion. Only one review of medical records of 89 patients with possible or proven PML showed an 18% prevalence of seizures [14]. These were noticed to have responded well to treatment and the seizures did not affect survival [14]. It is noteworthy that these two patients who presented with seizures were the only two patients with diagnosis of PML in our hospital. The inference is that seizures may not be a rare presentation in the Nigerian patients. Further studies will be needed to expound the common features of PML in the African patient. The presence of PML lesions immediately adjacent to the hemispheric cortex was the only risk factor associated with seizures[14]. In both cases, the

Changing Aetiologies of End Stage Kidney Disease in a Resource Poor Environment; What is the Way Forward?

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ABSTRACT

The prevalence of chronic kidney disease (CKD) is increasing worldwide. In most areas of Nigeria, chronic glomerulonephritis has been the most common documented aetiology of incident end-stage kidney disease (ESRD). We reviewed the causes of incident end-stage kidney disease in the last four years of operation. A trend test was performed to assess statistically significant changes in the incidence of the CKD aetiologies. Four hundred and forty nine incident ESRD patients, mean age 41.4 ± 16.3 years, presented over this period. HIV – related kidney diseases constituted 30.7% of the ESRD patients. This was followed by chronic glomerulonephritis (20.0%); hypertension (13.8%) and diabetes mellitus (13.6%) respectively. There was an increasing trend (p<0.001) of HIV – related kidney diseases over this period. It is expedient to initiate screening measures to detect early CKD among our HIV cohorts as many factors contribute to the development and progression of CKD in this population.

Keywords: Aetiology, ESRD, HIV-related nephropathy

INTRODUCTION

Chronic kidney disease and in fact, end stage kidney disease (ESKD) is a major public health problem globally. End stage kidney disease is the final common end point of many causes of chronic kidney disease. World over diabetes mellitus (DM) remains the leading cause of end stage kidney disease[1]. In developed countries DM and hypertension are the leading causes of chronic kidney disease, whereas in Sub-Saharan Africa, it mainly due to hypertension and chronic glomerulonephritis (CGN)[2]. In Nigeria, hypertension, chronic glomerulonephritis, chronic pyelonephritis and sickle cell nephropathy has been noted to be the leading cause of end stage kidney disease[2-4]. Diabetes mellitus has also been noted to be on the increase, now the third commonest cause of kidney failure in Nigeria[5]. The high prevalence of CGN in Nigeria was attributed to the high incidence of infective agents such as *Plasmodium malariae*, filarial worms, hepatitis B virus, *Schistosoma mansoni*, *Mycobacterium leprae* and streptococcal organisms[6]. Recently Human Immunodeficiency virus (HIV) has been found to be one leading cause of kidney disease, either directly or in association with others comorbidities[7].This may be attributed to the fact that Nigeria has second largest number of people living with HIV after South Africa.[8] Population changes in most developed countries suggest the potential for increase in the number of people with end stage kidney disease because the exponential increase in advanced age[9] , but the reverse may be the case in Nigerian where end stage kidney affect mostly younger population[2,5]

Most patients with CKD related to HIV in our environment are more likely to be younger and poorer, and therefore cannot sustain renal replacement therapy. This therefore underscores the need for early diagnosis and prevention of CKD among persons living with HIV. Earlier review of the first two years of haemodialysis in our centre revealed that CGN was leading cause of ESKD[10]. However recent observation showed HIV related kidney diseases may have assumed increasing importance as an aetiologic factor for ESKD in our environment, therefore we revisited the causes of ESKD in our centre.

METHODOLOGY

The dialysis centre of the University of Uyo Teaching Hospital is about 6 years old, having been established in 2008 to cater for the people of Cross River State and Akwa Ibom states with estimated population of 9 million people. The centre has 9 functional dialysis machines. This is retrospective study of all patients with end stage kidney disease who had haemodialysis from

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January 2010 to December 2013. Case notes of patients were retrieved, after getting approval from the Ethical Committee of the hospital. Socio-demographic data such age, sex, occupation, height, weight and marital status were extracted. Clinical characteristic such as blood pressure, fasting plasma glucose, biochemical and haematocrit levels, renal ultrasonographic findings and dialysis access routes and were extracted. Diagnoses were mainly clinical using history, age of subjects, laboratory findings and renal ultrasonography. We based our diagnosis on HIV history, age of subjects, laboratory findings and renal ultrasonography. We based our diagnosis on HIV positive status, findings of normal or enlarged kidneys size on renal ultrasonography and the present of nephrotic or sub-nephrotic range proteinuria[11]

Descriptive analysis of the characteristics of the patients was performed. Chi-square was used for comparison of categorical variables and the Wilcoxon rank sum test for continuous variables that were not normally distributed. Percentages for each of the aetiologies were reported. A trend test was performed to investigate any significant change in trend for each of the common aetiologies. All analysis was done using STATA 10, StataCorp, Texas USA.

RESULTS

A total of 449 incident ESRD patients were seen over the period. The mean age was 41.4 ± 16.3. Forty nine percent (49%) were female while 51% were male. Table 1 shows a progressive increase in the frequency of ESKD patients requiring dialysis in our centre.

Table 1: The percentage distribution of patient per year

Year of admission	Frequency	Percentage
2010	78	17.4
2011	107	23.8
2012	133	29.6
2013	131	29.3
Total	**449**	**100%**

HIV related kidney disease was the leading cause of ESKD contributing 30.7%. This was followed by chronic glomerulonephritis; hypertension and diabetes mellitus respectively (table 2). Conditions leading to obstructive uropathy occupied a distant fifth.

Table 2: The percentage distribution of the various aetiologic factors

Diagnosis	Frequency	Percentage
CGN	90	12.0
Hypertension	62	13.8
DM	61	13.8
HIV Related Kidney Disease	138	30.7
Obstructive Uropathy	29	6.5
Sickle Cell Disease	4	0.9
Alport's Syndrome	1	0.2
Chronic Rejection	1	0.2
Unknown	15	3.4
Missing Data	47	10.5
	449	100

Figure 1 shows the changing incidence of the aetiologic factors over the period of study. HIV related kidney diseases and obstructive uropathy appear to be increasing in incidence during the period of study. The mean systolic and diastolic blood pressure of those with HIV related kidney disease was also lower than other groups (figure 2). The mean age of those with HIV related kidney disease was 34.4±9.8years. This was significantly lower than that for hypertension 51.4±10.7 VS 34.4±9.8years, $p<0.001$. Diabetes mellitus (56.4±10.5 VS 34.4±9.8years), but higher than age at diagnosis for chronic glomerulonephritis (32.3±11.1VS 34.4±9.8years $p=0.04$). There was a significant increase in the frequency of incident HIV-related kidney disease as the years progressed (figure 3).

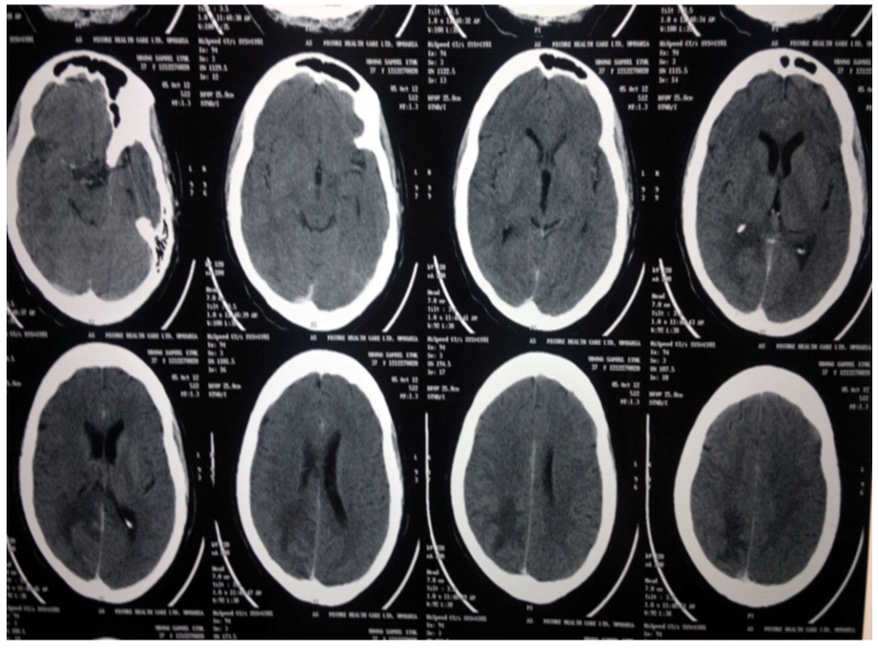

Fig 1: Brain CT scans of Case 1 showing non-enhancing hypodense white matter lesion in the right parieto-occipital region

admission, she developed right sided weakness. She had not commenced HAART despite being been diagnosed with HIV five years earlier. $CD4^+$ count was 19cells/uL. The Brain CT scan showed a non-enhancing hypodense white matter lesion in the right parieto-occipital region (see Fig. 1). A diagnosis of PML was made. She was commenced on HAART and carbamazepine 400mg bd. The seizures were completely controlled. She also had physiotherapy and therefore recovered enough to walk without support. She has been seen twice on follow-up and is doing well.

Case 2: This was a twenty three year old girl who presented with headaches, loss of consciousness and seizures six days after an appendectomy. Headache started two days earlier. There was associated loss of consciousness and frequent seizures. She presented in status epilepticus. There was a prior history of weight loss and non-specific headaches of one year duration. She was diagnosed HIV positive only one week prior to presentation. The HIV screen was carried out as part of routine work up for surgery (appendectomy).

A brain CT scan showed multifocal non-enhancing deep white matter at the level of the midbrain, thalamus and left fronto-parietal lobes with a subsequent diagnosis of PML. She was admitted into the intensive care unit. The seizures were controlled with diazepam infusion but she never recovered consciousness. She also had ceftriaxone, intravenous infusion, high protein diet from the naso- gastric tube. HAART was recommended since PML is an AIDS defining diagnosis confirming the disease to be a stage IV HIV disease. HAART however could not be commenced because of logistics reasons.She died on the twelfth day of admission. The cause of death was thought to be cerebral edema.

DISCUSSION

Progressive multifocal leukoencephalopathy (PML) is characterized by widespread demyelinating lesion due to infection by the JC virus. Prior to the advent of HIV, PML developed mostly in patients who had lymphoma, other malignancies and rare forms of immunosuppression[1]. The adventof HIV changed the face of PML such that more than 75 % is now

Progressive Multifocal Leukoencephalopathy Presenting with Seizures: A Report of Two Cases in Uyo, Southern Nigeria and a Review of Available Literature

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Abstract

Progressive multifocal leuko-encephalopathy (PML) is an opportunistic infection of the central nervous system that occurs almost exclusively in the setting of immunosuppression. It is a fatal demyelinating disease caused by the polyoma JC virus that commonly presents with impaired vision, mental changes and motor weakness. Seizures are a rare presentation. We report two cases that presented with seizures. This to the best of our knowledge is the first report in Africa. We report the cases of two women ages thirty five and twenty three years respectively who presented with seizures. The first woman had left sided seizures, loss of consciousness with associated weakness of the left side of the body. She had been HIV positive for five years but had not commenced HAART. The second patient presented with frequent seizures which was preceded by headaches and loss of consciousness. She had been diagnosed HIV positive only a week earlier but had a history of weight loss and nonspecific headaches for one year duration. Brain CT scan showed features consistent with PML in both cases. PML is not a rare disease in HIV patients. The presentation however may be unusual as described in these two patients. There is need for a high index of suspicion. The acquisition of modern imaging modalities has contributed immensely to increased diagnosis of cases.

Keywords: HIV, PML, Rare, Seizures, Nigeria

INTRODUCTION

Progressive multifocal leuko-encephalopathy (PML) is an opportunistic infection of the central nervous system. It is a fatal demyelinating disease characterized by widespread lesions due infection of the oligodendrocytes by the human papovavirus. This virus was identified as the etiological agent in 1967 from by John Cunningham and named JC virus after him in 1971 [1]. PML occurs almost exclusively in immunosuppressed individuals such as patients with HIV/AIDS, haematological and lymphoreticular malignancies, rheumatological diseases or persons undergoing organ transplantation. It has also been reported in patients receiving monoclonal antibodies and various other immune suppressants [1].

PML is associated with both HIV-1 and HIV-2 [2,3]. HIV infection accounts for almost 85% of the total cases. Presently it is one of the AIDS-defining illnesses in HIV- infected patients. Patients with progressive multifocal leukoencephalopathy (PML) typically experience insidious onset and steady progression of focal symptoms that include behavioral, speech, cognitive, motor and visual impairment [4]. Persons with more preserved immune status may show a slower progression of the disease than those with an immunocompromised state. Seizures are considered a rare manifestation but studies have shown that many patients with seizures had demyelinating lesions adjacent to the cortex. We report two cases that presented with seizures.

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CASE REPORTS

Case 1: The patient was a thirty five year old female nurse who presented seizures, loss of consciousness and weakness of the left side of the body. The seizures were focal involving the left upper and lower limbs with tonic eye and neck deviation. There was associated brief loss of consciousness. On recovery of consciousness, there was headache, vomiting and weakness of the left side of the body. Initial episode of seizures (which took place five days earlier) could not be characterized as it happened in the market.

However, there was associated urinary and fecal incontinence with a post ictal sleep of 3 hours duration. One month later, while still on

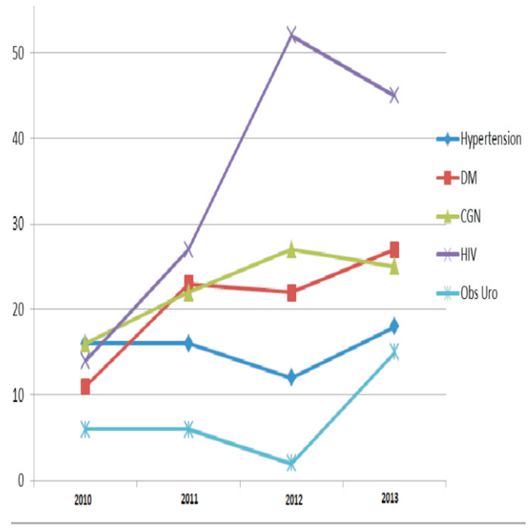

Figure 1:Changing Trend of ESKD Aetiologies

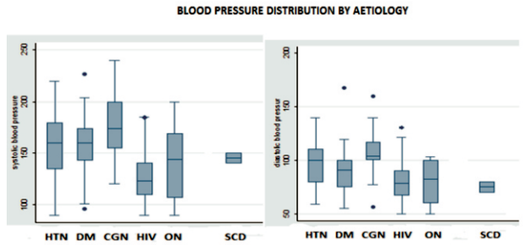

Figure 2: Blood pressure distribution

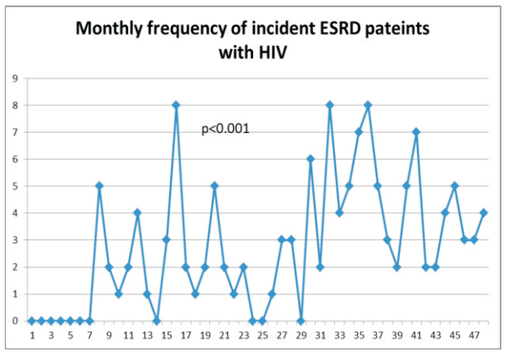

Figure 3: Showing Monthly trend in Diagnosis HIV Related Kidney Disease

DISCUSSION

This review revealed a progressive increased in the number of new patients with end stage kidney disease. An average of nine new patients was admitted per month for renal replacement therapy within the period under review. This is against an average of 4 patients per month which was the case in the first two year of the establishment of our centre [10]. This may be due to increased awareness of kidney diseases or it may be because we were not dialysing HIV positive patients in the first two years of our existence.

The commonest cause of end stage kidney disease in this review was HIV related kidney disease. We choose to called it HIV related kidney disease because renal biopsy were not done due to the retrospective nature of the study, therefore we could not conclusively claimed that we were dealing HIV associated nephropathy (HIVAN). HIVAN is a form of CGN, often characterized by focal segmental glomerular sclerosis of the collapsing variants.

HIV Associated Nephropathy has been shown to be one of leading cause of ESKD among the African American.[12] Kidney is one of the major organs affected early in the course of HIV infection. It is now widely recognized as a frequent complication of HIV infection[13]. Other causes of kidney disease include HIV- related immune complex disease; nephropathy secondary to antiretroviral therapy (ART) or antibiotics and thrombotic microangiopathy [14].

The prevalence of chronic kidney disease (CKD) in HIV patients ranges from 3.5% to 32.6%, depending on the characteristics of the study population and the criterion used in defining CKD.[15,16] In USA, dipstick proteinuria of≥1+ was found in 32.6% of patients, 7.2 % have renal disease at baseline while 14% of patients developed renal insufficiency after 21months.[16] In Europe CKD is seen in 3.5% of HIV patients using Cockcroft-Gault and 4.7% using MDRD formulae.[16] Also in Kenya proteinuria of ≥1+ was found in 6.2% of HIV patients without risk factor for kidney disease, while in China it is 16.8%.[17,18] In Nigeria Chioma et al found 38% of HIV had proteinuria[7].

In our review, patients with HIV related kidney disease had lower blood pressure compared with those who had CGN, Hypertensive nephropathy or Diabetic nephropathy (Fig 4 and5). This was consistent with the normal blood pressure findings in HIVAN patients.[11]

Although patients with HIVAN usually have rapid progression to ESKD, it has been shown that if diagnosis is made early and treatment with highly active anti-retroviral therapy initiated, the progression maybe retarded or delayed[19]. This