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Pattern of neurological complications of chronic myeloid leukaemia in Ilorin, Nigeria: A ten year review

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Abstract

Aim and Objective: The study was carried out to document the pattern of neurological complications seen in patients with chronic myeloid leukemia who were managed at the University of Ilorin Teaching Hospital, Ilorin and compare with previous reports from other parts of Nigeria and elsewhere.
Materials and Methods: A ten year retrospective analysis of all cases of CML managed at the study centre between January 2006 and December 2015 was carried out. Case folders of all patients diagnosed with CML during the study period, and the Malignancy registers of the Haematology department were retrieved and analyzed. Relevant information retrieved included age, gender, clinical features at presentation, laboratory investigations, treatment regimen, and survival outcome among others.
Results: Thirty six (36) patients were diagnosed with CML during the study period. There were 21 (58.3%) males and 15 (41.7%) females, giving a male: female ratio of 1.4:1.The mean age of the patients at diagnosis was 37.5 years (range, 11-75 years). Nine (25%) patients presented with various forms of neurological complications and the mean WBC count in them was 383.2 x 10^9/L (280.5 – 601.0 x 10^9/L). Auditory complications were the commonest neurological deficits found in 6(66.7%) of the 9 patients with neurological manifestations.
Conclusion: The neurological complications recorded in this study were similar to those reported in previous studies from Nigeria and other countries. These complications need to be looked for at presentation and adequately characterized as their presence could significantly influence the prognosis of the disease and decisions on management modalities.

Keywords: Pattern, Neurological, Complications, CML, Nigeria

Introduction

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder of the pluripotent stem cells in the bone marrow and is characterized by uncontrolled proliferation of myeloid progenitor cells thereby leading to accumulation of myeloid cells at various stages of differentiation in both marrow and peripheral blood [1,2]. More than half of patients with CML are often discovered accidentally from routine full blood count examination for other unrelated ailments which then reveal markedly elevated white blood cell count; or when an enlarged spleen and/or hepatomegaly is found on abdominal examination.

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The worldwide annual incidence of CML has been estimated at approximately 10 cases/million population, with a median age of occurrence of 50-65 years in the Western world[3, 4]. In Nigeria, age range of 12-74 years with a median of 38 years had been reported [5].

Chronic myeloid leukemia is associated with a specific cytogenetic abnormality, the Philadelphia (Ph) chromosome which was first described by Peter C. Nowell and David Hungerford in the blood and bone marrow cells of patients with CML in 1960 [6]. The Ph chromosome, t (9;22) (q34;p11), is formed from a reciprocal translocation with juxtaposition of genetic materials between the long arms of chromosomes 9 and 22. The Abelson (Abl) oncogene on chromosome 9 becomes translocated to the Break point cluster (Bcr) region on chromosome 22 to form the Bcr/Abl chimeric gene. The BCR-ABL gene encodes a protein with

deregulated tyrosine kinase activity which then causes uncontrolled production of myeloid cells in the bone marrow and their accumulation in the peripheral blood. The normal production of other cellular elements such as red blood cells and platelets in the marrow is also suppressed by the myeloid hyperplasia, and the infiltration of certain organs in the body by the myeloid cells gives rise to some of the presenting features of CML [2,4].

Hyperleucocytosis (white blood cell count >100 x 10^9/L) which is present in many CML patients causes increased blood viscosity with impairment of blood flow in the microcirculation (leucostasis) causing vascular occlusion thereby resulting in ischaemia, haemorrhage and oedema of the involved organs [7]. About 15-25% of patients with CML have been reported to present with clinically significant morbidity and mortality from leukaemic hyperleucocytosis and leucostasis [4,7,8,9]. Neurological complications of CML are said to be rare and are responsive to cytoreductive therapy with Hydroxyurea, Busulphan, Imatinib mesylate and leukapheresis [4,7].

The complications which have been reported in CML patients due to hyperleucocytosis and leucostasis include central nervous system (CNS) involvement – (dizziness, slurring of speech, aphasia, delirium, stupor , intracranial haemorrhage), Visual involvement – (visual blurring, papilloedema, diplopia, retinal haemorrhage, blindness), Ear involvement – (tinnitus, partial hearing loss, complete deafnes)s, and Penile involvement – (priapsm), and gait abnormalities – (ataxia, paresis, paraplegia) [7].

Hearing impairment or loss had been reported as the most common neurological complications associated with CML [7,10,11,12,13]. Sanyaolu et al [10] in Ile-Ife, Nigeria reported that 69.2% of CML patients in their study had bilateral hearing impairment, while 30.8% had unilateral hearing loss. Onwukeme et al [14] in Jos, Nigeria also reported sensori-neural hearing impairment in 5(50%) of the 10 CML patients in their study. Several other studies from within Nigeria and elsewhere have reported hearing loss and impairment in patients with CML[4,7,10,13,15].

Ophthalmic complications such as visual blurring and blindness alone or in combination with hearing loss or other forms of sensori-neural deficits had been reported in many studies [4,7,16,17]. Eze et al [16] in Enugu, Nigeria reported ophthalmic complications in 77.8% of adults with leukaemia in their study, while Aken'Ova et al [17] reported blindness, deafness and paraplegia in a 16 year old female CML patient seen at the University College Hospital (UCH) in Ibadan, Nigeria.

Speech abnormalities such as dysarthria, slurring of speech and aphasia although said to be rare complications of CML or other myloproliferative diseases have been reported by Janssen et al [18] and Yeung et al [19].

Priapsm was reported by several authors as a complication of CML [20,21,22,23,24,25,26]. The incidence of priapsm was reported to be about 1-2% in male patients with CML [20]. Tazi I [21] reported priapsm as the first presenting feature in a 33 year old Morrocan man diagnosed with CML. Also, Ocheni S et al [25] in Enugu, Nigeria reported priapsm in 2 patients with CML in their study.

Neuromuscular complications like ataxia, paresis and paraplegia had also been reported in CML patients [17,18]

From literature search and review of previous studies or reports which documented the various types of neurological or sensori-neural complications associated with CML, there were several case reports, which described specific types of neurological complications [4,10,11,12,16,17] mentioned above but there was paucity of studies which documented the pattern of the various neurological complications in groups of CML patients. Only two studies from Nigeria were found which documented the pattern of sensori-neural complications of CML in their study groups [7, 14]. The main aim of this study, therefore, was to review and document the pattern of neurological complications found in CML patients who were diagnosed and managed at the Department of Haematology of University of Ilorin Teaching Hospital, Ilorin, Nigeria over a ten year period and compare with previous reports from within and outside Nigeria.

Material and Methods

This is a retrospective study of all cases of chronic myeloid leukemia which were diagnosed and managed at the Haematology Department of University of Ilorin Teaching Hospital, Ilorin, Nigeria from 1st January 2006 to 31st December 2015 inclusive.

The materials used for the study consisted of patients' case folders and the Haematology Malignancy registers from which pertinent information such as the bio-data,

clinical features at presentation, laboratory investigation results (peripheral blood and bone marrow report forms), treatment regimen and outcome etc were retrieved and recorded. All the patients included in this study had peripheral blood counts and bone marrow aspiration done in order to make the diagnosis of CML. All the bone marrow and peripheral blood films were prepared using standard haematology procedures described by Dacie and Lewis [27]. The final diagnosis was arrived at by consensus among the Consultants and Senior Residents in the Department. Following diagnosis, some of the patients were referred to the Department of Haematology and Immunology, Obafemi Awolowo University Teaching Hospital, Ile-Ife, Nigeria, which has facilities for Karyotyping in order to determine their Philadelphia chromosomal status and suitability for enrolment in the Glivec Treatment program offered by the Institution. Other investigations which guided us in the diagnosis and management of the patients included – serum electrolytes and urea, liver function tests and abdominal ultrasound scan. All the patients who presented with symptoms and signs suggestive of neurological or sensori-neural impairments were appropriately referred to Consultants/Specialists in the relevant departments for proper assessment and documentation.

All the patients were admitted at presentation for investigation, rehydration and commencement of cytoreductive therapy with Hydroxyurea or Busulphan once the diagnosis was made. Allopurinol was added to the treatment regimen to prevent the complications of tumor lysis syndrome that could result from destruction of the malignant white blood cells. Red blood cell and platelet concentrate transfusions were offered to the patients when indicated. The patients were discharged from the hospital following satisfactory reduction in WBC and improvement in clinical status and then followed up at the Haematology Clinic and Day Care centre of the Department.

Also, available literature were searched and reviewed on the subject matter and documented. The data which were generated from the case folders and other sources were entered into SPSS Statistical Package software version 21 and analysed and results presented in form in frequency tables.

Results

Thirty six cases of CML were seen and managed at the Haematology Department of University of Ilorin Teaching Hospital, Ilorin, Nigeria within the study period. There were 21(58.3%) males and 15(41.7%) females giving a male: female ratio of 1.4:1(Table 1).The mean age of the patients at diagnosis was 37.5 years (range 11 – 75 years). The mean total White blood cell count (WBC) for all the patients was 203.7 x 10^9/L (range 24.1 x 10^9/L – 601.0 x 10^9/L). Nine (25%) patients presented with one or more neurological complications at the time of diagnosis. The mean WBC in the nine patients with neurological complications was 383.2 x 10^9/L (range 280.5 x 10^9/L – 601.0 x 10^9/L) – Table 2.

Table 1: showing the annual and sex distribution of the 36 CML patients who were managed at U.I.T.H, Ilorin during the study period

Year of Diagnosis	Males (%)	Females (%)	Total (%)
2006	**1**	**2**	**3**
2007	**1**	**1**	**2**
2008	**2**	**2**	**4**
2009	**1**	**2**	**3**
2010	**2**	**2**	**4**
2011	**3**	**1**	**4**
2012	**2**	**1**	**3**
2013	**3**	**1**	**4**
2014	**2**	**2**	**4**
2015	**4**	**1**	**5**
TOTAL	**21 (58.3)**	**15 (41.7)**	**36 (100)**

*M: F ratio = 1.4:1

Out of the nine patients with neurological complications, two (22.2%) presented with bilateral hearing loss, two (22.2%) had left ear hearing impairment with tinnitus, and one (11.1%) had right ear hearing impairment with tinnitus. One patient (11.1%) presented with bilateral hearing impairment, tinnitus and gait ataxia, another patient (11.1%) had gait ataxia with lumbar spondylosis, and another patient (11.1%) had bilateral visual blurring with demonstrable leukaemic deposits on the retina by fundoscopy. Aphasia was seen in one patient (11.1%). (Table3). Other causes of blindness or hearing loss or impairment such as trauma or foreign body in the ear were excluded in the patients who presented with such features.

Table 2: showing the clinical and laboratory features of the 9 CML patients with neurological complications in U.I.T.H, Ilorin as recorded at Diagnosis.

Case No.	Sex	Age (Years)	Spleen size (cm)	Liver size (cm)	PCV (%)	WBC (x 10^9/L)	Platelet (x10^9/L)
1.	**M**	**43**	**16**	**6**	**26**	**290.0**	**184**
2.	**M**	**33**	**18**	**6**	**30**	**500.0**	**125**
3.	**F**	**57**	**14**	**4**	**34**	**286.1**	**429**
4.	**M**	**60**	**16**	**5**	**20**	**601.0**	**118**
5.	**F**	**48**	**13**	**6**	**31**	**348.0**	**215**
6.	**F**	**75**	**20**	**5**	**29**	**280.5**	**182**
7.	**M**	**25**	**18**	**8**	**31**	**288.0**	**290**
8.	**M**	**52**	**22**	**10**	**25**	**460.5**	**402**
9.	**F**	**37**	**14**	**6**	**28**	**395.0**	**103**

*Mean WBC = 383.2 x 10^9/L

Table 3: Showing the prevalence of neurological complications among the 9 CML patients seen during the study period

Types of Neurological Complications	Prevalence (% of 9 patients)
Bilateral deafness	**2 (22.2)**
Left ear hearing impairment + Tinnitus	**2 (22.2)**
Right ear hearing impairment + Tinnitus	**1 (11.1)**
Bilateral hearing impairment + Tinnitus + Ataxia	**1 (11.1)**
Ataxia + Lumbar spondylosis	**1 (11.1)**
Visual Impairment	**1 (11.1)**
Aphasia	**1 (11.1)**
Total Number of patients	**9 (100)**

Auditory complications were the commonest neurological complications seen in the CML patients which was recorded in six (66.7%) of the nine patients. Following the cytoreductive chemotherapy with Busulphan or Hydroxyurea, most patients achieved clinical and haematological controls of the disease within 4-6 weeks with significant reduction in splenic or liver sizes, and return of WBC to less than 20 x 10^9/L. Leukapharesis was not done for any of the patients with hyperleucocytosis due to lack of facilities for the procedure. In all the patients with neurological impairments, no significant improvements in visual, auditory or speech defects were observed despite control of WBC counts.

Discussion

Chronic myeloid leukemia is a clonal myeloproliferative disease of the bone marrow pluripotent stem cells characterized by an uncontrolled proliferation of myeloid progenitor cells and accumulation of all stages of myeloid cells maturation in the peripheral blood [1]. The disease is believed to arise from the formation of the Philadelphia chromosome, t(9;22)(q34,q11) due to a reciprocal translocation of Abl oncogene on the long arm of chromosome 9 to the Bcr region on the long arm of chromosome 22 resulting in the production of an aberrant Tyrosine Kinase which drives the excessive proliferation of the myeloid cells in the marrow with inhibition of apoptosis to cause the peripheral blood accumulation of the malignant cells [2, 4].

CML was reported to constitute about 14% of all leukemias worldwide and 20% of adult leukaemias with a median age of occurrence of 65 years in Caucasians [3, 4], and 38 years among Nigerians [5] .The mean age of the CML patients at presentation in our study was 37.5 years, which was close to the median age reported in a previous study from Ile-Ife, Nigeria by Boma et al [5]. A previous study from Ilorin, Nigeria also reported a mean age of 38.3 years in a cohort of 46 CML patients studied [28].

The prevalence of CML was found to be slightly higher in males than females in our study (male: female ratio was 1.4:1). This finding was in agreement with the study of Joseph et al in Jos, Nigeria [7].

Hearing defects in the form of tinnitus, impairment, partial or complete deafness had been reported in literature as the commonest form of neurological complication associated with CML [4,7,10, 11,14, 15,17], which could be unilateral or bilateral, and may occur in association with other forms of neurological deficits in the same patient. Many studies documented hearing impairment or loss as the first presenting feature of CML in their studies[4,7,14,29] . In the present study, auditory complications were found in 6 (66.7%) out of the nine patients with neurological complications, and the defects

were present at the time of diagnosis. This finding was also in agreement other previous studies from within and outside Nigeria which found hearing defects as the commonest presenting feature in their CML patients[7,10,14,30]. Joseph et al [7] in Jos, Nigeria, reported that the left ear was more vulnerable to neurological involvement in their study. However, in our study, bilateral ear involvement was found to be higher (33.3%) in the CML patients with neurological complications in contrast to the finding from Jos but was lower than the 69.2% bilateral ear involvement reported by Sanyaolu et al [10] in Ile-Ife, Nigeria. Tinnitus was found in all the patients with hearing loss or impairment in our study, a finding which was also reported by Sanyaolu et al [10].

Opthalmic complication in the form of bilateral visual blurring and difficulty seeing close and distant objects clearly were the presenting complaints in one patient in our study. Visual acuity (VA) done for the patient revealed reduced vision in both eyes with VA in left eye being 4/12 and right eye 6/12, and fundoscopic examination done also showed leukemic infiltrates of the retina in both eyes. Visual impairment in the form of blurring of vision, reduced visual acuity or blindness had also been reported by many authors[4,7,16,17,31]. In Jos, Nigeria, Joseph et al[7] found bilateral blindness in a patient who also had leukemic deposits on the retina on fundoscopic examination. Also in Port Harcourt, Nigeria, Ejele et al[4] reported visual and auditory impairments in a pregnant woman with CML at presentation, and fundoscopy showed bilateral patchy areas of ischaemia and blot haemorrhages on the retina. The bilateral visual impairment which was present in only one patient in our study failed to resolve in spite of cytoreductive therapy, an observation was also reported by Joseph et al [7].

Aphasia and dysarthria have also been reported in patients with CML[18.19]. We encountered a patient who presented with aphasia and incoherent speech in our study. Aphasia as a complication of CML is said to be rare and few case reports were found during the literature search. Janssen et al [18] reported aphasia in association with deafness and hearing loss in a 51 year old CML patient. Yeung et al [19] also reported expressive aphasia in a patient with chronic myelomonocytic leukemia. The finding of aphasia in a patient in this study is in agreement with previous case reports of aphasia as a complication of CML.

Gait ataxia was also recorded in 2 patients in our study. Although, no case of ataxia had been reported previously in Nigeria, a few cases from other parts of the world had been recorded in CML patients[18,33,34]. The finding of ataxia in 2 patients in our study corroborated previous reports from outside Nigeria and should be borne in mind as a possible complication of CML in our environment.

Priapism had also been reported by several authors as a complication of CML[20,21,22,23,24,25,26], but no single case of priapism was recorded in our study.

Hyperleucocytosis (WBC> 100 x 10^9/L) is a common feature in CML patients worldwide, and several studies had documented this phenomenon as the most probable cause of the neurological complications found in patients with CML [4,7,8,9,35].The resultant hyperviscosity syndrome and leucostasis from the hyperleucocytosis cause impaired blood flow in the microcirculation with reduced blood supply to the organs and tissues causing focal ischaemia, haemorrhage and oedema in the affected organs and tissues, and when the central nervous system (CNS) is involved can produce the observed neurological deficits associated with the myeloproliferative disorders, CML inclusive[19].

All the nine patients in our study who had neurological complications had hyperleucocytosis with mean total WBC of 383.2 x 10^9/L (range, 280.5 x 10^9/L – 601.0 x 10^9/L). Our finding is similar to the reports of Ejele et al[4] and Joseph et al[7] which also documented hyperleucytosis, hyperviscosity and leucostasis as the possible pathogenic mechanism for the neurological complications seen in their patients. However, in the report of Joseph et al[7], the WBC counts at which they observed the neurological complications in their patients was much lower (105 – 150 x 10^9/L) compared to the mean WBC count of 383.2 x10^9/L (280.5 – 601.0 x 10^9/L) in our study.

In theory, treatment of CML patients with cytoreductive drugs and the return of WBC count to normal or near normal levels should improve or reverse the neurological symptoms. However, in our study in spite of the good control of WBC count achieved with the cytoreductive therapy, neurological deficits in the patients were not improved or reversed. Joseph et al [7] also did not record any improvement in the neurological symptoms in their patients following cytoreductive therapy, and suggested that there may be a yet to be identified mechanism which

contributes to the popular theory of leucostasis and hyperviscosity in the development of neurological complications in CML.

Leukapheresis is a treatment option which can be used when there is hyperleucocytosis in CML patients [36], and it can effectively achieve a rapid reduction in WBC count. None of the patients in our study had leukapheresis due to lack of this facility in our centre, but all the patients were treated with Hydroxyurea ,Busulphan or Imatinib mesylate (Glivec, in a few cases that were enrolled in the Glivec Treatment programme at the OAUTH, Ile-Ife, Nigeria). All the patients achieved significant control of WBC counts within 4-6 weeks and were discharged and subsequently followed up in the Haematology Outpatient Clinic and Day Care centre.

Although, it is said that neurological complications in CML are rare, only a few studies had documented the pattern of such complications in groups of CML patients. This study had, therefore, documented the pattern of neurological deficits that were encountered in a cohort of 36 CML patients in our centre, and compared with findings in similar studies. There is the need for greater vigilance on the part of all concerned in the diagnosis and management of these patients to adequately investigate patients for early detection of any such complications as this will greatly influence decisions on the management and prognosis of the patients.

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