JOURNAL OF KENYA ASSOCIATION OF PHYSICIANS

September 2019 Vol 2 No. 2 ISSN 2663-6484

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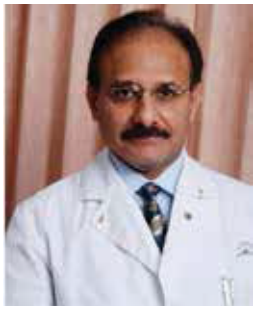

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Published by Kenya Association of Physicians
P.O. Box 48397 Code 00100, Nairobi, Kenya. www.kapkenya.org

Editorial

Postgraduate Training in Internal Medicine in the East Central Southern African Region

Postgraduate training in Internal Medicine should be designed to produce a professional who ultimately attains appropriate competencies and skills to manage patients at a consultant level and be an excellent communicator. The physician should be research-oriented, be a critical thinker and provide leadership in healthcare systems. The training programme should incorporate quality improvement concepts in patient-centred clinical care.

The 21st century physician, should have attributes that facilitate holistic patient care. The physician should be able to demonstrate the following abilities: understand and internalise concepts in epidemiology and disease processes, make an accurate clinical diagnosis and plan management of acute, and chronic medical conditions. The physician should provide group-leadership in multidisciplinary patient care teams. The physician should demonstrate the ability to teach and train various cadres of healthcare personnel, understand the professional and ethical practice of medicine and the legal framework that guides it, efficiently use medical informatics in patient care and research, and formulate health care policy, and practice efficient resource management in healthcare systems.

Kenya has a population of close to 50 million (1) and currently has about 400 registered physicians; i.e. holders of MMED internal medicine or its equivalent qualification. Four hundred is the total number of physicians who are registered by the Kenya Medical Practitioners and Dentists Council. This number excludes attrition through relocation, retirement, or death. Attrition factors may result in approximately 75% of the total number of physicians who are in active practice. A significant proportion of these physicians are clustered in urban centres such as Nairobi, Mombasa, Kisumu, Eldoret and Nakuru. The current annual output of physicians is about thirty from the three universities in the country that offer the MMED internal medicine programme. The World Health Organization target number is 5 physicians/100,000 inhabitants; Kenya has less than 1 physician/100,000 inhabitants. Kenya, therefore, requires 2,500 physicians today. Lack of an adequate number of training sites for physicians in Kenya makes it imperative that other forum of training of physicians, such as collegiate training should be embraced.

The statistics are not very different in neighbouring countries. Tanzania has a population of about 60 million with approximately 108 physicians, Uganda population of about 44 million, and about 280 physicians, Malawi population of about 20 million and about 25 physicians, Zambia population of about 20 million and about 80 physicians, and Zimbabwe population of about 20 million and 100 physicians. The six-country region has a population of about 200 million and specialist physician population of about 1100. Going by the current World Health Organization target of 5 physicians /100,000 inhabitants, clearly, there is a gross disparity in the whole region. If one goes by the WHO recommendation, the region would need about 10,0000 physicians. The current statistics indicate that the region has about 5 physicians/ 900,000 inhabitants (2).

The growing double burden of infectious diseases and Non-Communicable Diseases compounds the scenario. The six-country region, i.e. Kenya, Tanzania, Uganda, Malawi, Zambia and Zimbabwe have about 21 Universities that have postgraduate training in internal medicine. Kenya has 3 universities, Uganda has 4 universities, Tanzania has 4 universities, Malawi has 1 university, Zambia has 3 universities, and Zimbabwe has 2 universities. The annual output of well-trained physicians in the region is grossly inadequate as per WHO estimates (2).

To address this disparity of training of physicians in the region, an incredibly noble concept was realized by the formation of East Central Southern Africa College of Physicians (ECSACOP). This was as a consequence of the 52nd Health Ministers Conference held in Harare, Zimbabwe in 2010 that established the ECSA College of Health Sciences with autonomous constituent professional colleges. ECSACOP is a constituent professional college of ECSA College of Health Sciences. The College of Health Sciences has six constituent colleges that have so far been established since 2010. This has enhanced postgraduate training in general in various other medical disciplines. The constituent colleges include: The East Central and Southern Africa College of Nurses (ECSACON), The College of Surgeons of East Central and Southern Africa (COSECSA), The College of Ophthalmology of Eastern, Central and Southern Africa (COECSA), The College of Pathologists of East, Central and Southern Africa (COPECSA), The College of Anesthesiologists of East, Central and Southern Africa (CANECSA), and The East Central Southern Africa College of Physicians (ECSACOP) .

The East Central Southern Africa College of Physicians (ECSACOP) training programme commenced in Zimbabwe, Zambia in 2018, and is due to begin in Malawi and Uganda in September

2019. Plans for the programme to start in Kenya and Tanzania in September 2020 are ongoing.

Both University training model and Collegiate training model have a complementary role in ensuring that the region has a sufficient number of well-trained physicians and ought to operate in tandem.

Special gratitude for the formation of ECSACOP goes to the Royal College of Physicians (RCP London) as the leading champion, sponsor. Special mention goes to Professor Keith McAdam, who has been extremely instrumental in the whole process of establishment of ECSACOP. The implementation process continues to be championed by the current President of RCP London Professor Andrew Goddard and the present Chief Executive Officer RCP London, Dr Ian Bullock.

We should strive to provide patient-centred care to the inhabitants of Kenya and the region. A significant prerequisite for success is to establish excellent training models at sites that are distributed equitably in the region. Collegiate training is best poised to achieve this goal.

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Original paper

Helicobacter Pylori Culture Rate and Antibiotic Resistance Patterns among patients with Dyspepsia at Moi Teaching and Referral Hospital, Eldoret, Kenya

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Abstract

Background: *Helicobacter pylori* (*H. pylori*) infection is associated with upper gastrointestinal diseases including peptic ulcer disease, gastritis, gastric adenocarcinoma and mucosal associated lymphoid tissue lymphoma. *H. pylori* is a fastidious organism and thus difficult to culture especially after prolonged time between sample extraction and start of the culture. Triple therapy eradication regimens are available with little data on current antibiotic sensitivity patterns.

Objective: To determine the *H. pylori* culture rate and resistance patterns following 20 to 24 hour transportation in normal saline at Moi Teaching and Referral Hospital (MTRH).

Design: Cross-sectional descriptive study.

Methods: Participants aged 18 years and above referred for endoscopy due to dyspepsia were consecutively enrolled until the desired sample size was achieved. Participants underwent endoscopy during which biopsies were taken, two each from the gastric antrum and corpus. Rapid Urease Test (RUT) for *H. pylori* was done on one sample each from the antrum and corpus. For the samples that tested positive, their pair samples were put in normal saline and packed in ice in a cooler box and sent for *H. pylori* culture within 20 to 24 hours on brain heart infusion agar and subsequent antibiotic susceptibility testing.

Results: Between April 2014 and February 2015, 634 patients were screened of which 156 were enrolled to the study and subsequently underwent endoscopy, gastric biopsy and RUT. The enrolled participants had a median age of 41 (IQR: 28-58) years; and comprised of 64 (41%) males. The main indication for endoscopy was epigastric pains, seen in 151 (97%) of patients. Forty two (27%) of participants had previously received treatment for dyspepsia with either a proton pump inhibitor, histamine receptor type 2 blocker or anti *H. pylori* antibiotics. Eighty three (53%) had a positive RUT. Culture was done on 69 samples that reached the laboratory within 24 hours. *H. pylori* was isolated in 9 (13%) samples. All the 9 strains of *H. pylori* isolated were resistant to metronidazole. There was no resistance to clarithromycin.

Conclusion and recommendations: The culture rate of *H. pylori* following 20 to 24 hour delay was low. All the *H. pylori strains* isolated were resistant to metronidazole. Culture of *H. pylori* after 20-24 hour transportation in normal saline is not useful. A comparative study to determine the optimal transportation time and transport media is recommended. Clarithromycin based therapies without metronidazole is appropriate for *H. pylori* eradication regimens.

Key words: Helicobacter pylori, Culture, Antibiotic resistance, Resistance

Introduction

Helicobacter pylori (H. pylori) is a microaerophilic gram negative bacterium that colonizes the gastric mucosa. It's associated with development chronic gastritis, peptic ulcer disease, gastric adenocarcinoma, and Mucosa Associated Lymphoid Tissue (MALT) lymphoma (1-4). It is estimated that more than half of the world's population is infected with *H. pylori* (5).

Despite its unique role in the management of *H. pylori*, culture is not used routinely because of various factors: special conditions for transportation, urgency of specimen processing, expensive and complicated media, special incubation conditions and duration of culture (6). Regardless of these challenges culture is particularly useful because of the prospect of doing antibiotic susceptibility testing in patients who have used two courses of different antibiotic eradication regimes without cure (7).

Several factors affect *H. pylori* culture isolation rate: Recent use of antibiotic and proton pump inhibitors; prolonged time between specimen extraction and processing; choice of transport media; number and site of biopsies taken, provision of micro aerophilic environment for culture, duration of culture and use of selective media (8).

Samples have been processed after 24 hours of extraction without significant loss to diagnostic yield (9). The prospect of doing successful cultures following up to 24 hours delay from sample extraction provides an opportunity for centres unable to undertake cultures to transport samples for up to 24 hours to central laboratories where cultures can be undertaken.

Several transport media have been used for *Helicobacter pylori* with success. These include: Colombia blood agar, Brain Heart Infusion agar, brucella broth, cysteine albimi (10,11). Normal saline has been used successfully as a transport media without significantly affecting the isolation rate, providing a cheap transport media in resource poor settings (9). The choice of culture media also impacts on isolation rate of *H. pylori*. In a study that compared the culture media, the isolation rates were: Brain Heart Infusion Agar (96%), trypticase Soy agar (78%), Egg Yolk Agar (64%) and Colombia Blood Agar (32%) (12).

The main objective of this study was to determine the culture rate and antibiotic resistance patterns of *Helicobacter pylori* following 20-24 hour transportation time of specimens in normal saline among patients with dyspepsia at Moi Teaching and Referral Hospital. Secondary objective was to determine the current prevalence of *H. pylori* at MTRH.

Materials and methods

This was a cross-sectional descriptive study among patients with dyspepsia referred for upper gastrointestinal endoscopy at Moi Teaching and Referral Hospital, Uasin Gishu County, Kenya. Cultures were done at Pathologists Lancet Kenya Limited, a South African National Accreditation System (SANAS) accredited laboratory on 5th Avenue Office Suites, Upper Hill, Nairobi.

Consecutive sampling of patients who met the study criteria was done until the required minimum sample size of 126 was achieved for both prevalence and culture rate. Inclusion criteria included patients aged 18 years and above with symptoms of dyspepsia and not on PPI, H2R blockers or any antibiotic in the preceding two weeks before endoscopy. Failure to intubate the stomach or give consent resulted into exclusion. Informed written consent was obtained from all participants.

At endoscopy, 4 gastric mucosal forceps biopsies (2 from the antrum and 2 from the corpus) were obtained. Two (one each from the antrum and corpus) of the four gastric biopsies were immediately tested for active *H. pylori* infection using the rapid urease test (Esokit Hp Test). Patients whose rapid urease test turned positive within four hours had the other two gastric biopsies put in one milliliter of normal saline and transported overnight in a cooler box to Pathologists Lancet Kenya, Nairobi where the samples were cultured the following day at 9: 00am.

In the laboratory, *H. pylori* were cultured in selective Brain Heart Infusion Agar under microaerophilic conditions. Epsilometer (E) test strips were applied for clarithromycin, metronidazole, amoxicillin and tetracycline and incubated for a further 24-36 hours in non-selective culture media before the Minimum Inhibitory Concentrations (MICs) for each antibiotic was read.

MIC levels that were interpreted as sensitive were less than or equal to 0.25µg/ml for clarithromycin and amoxicillin, less than or equal to 2µg/ml for tetracycline and metronidazole. On the other hand MIC levels that were interpreted as resistant were equal or more than 1µg/ml for clarithromycin and amoxicillin, equal or more than 4µg/ml for tetracycline and equal or more than 8µg/ml for metronidazole. These MIC breakpoints specifically determined for *Helicobacter pylori* were based on Clinical Laboratory Standards Institute guidelines for clarithromycin and an updated appraisal for the rest of the antibiotics (13,14). MIC levels between susceptible and resistant break points for each antibiotic were regarded as intermediate. Data was analyzed using STATA version 13 special edition.

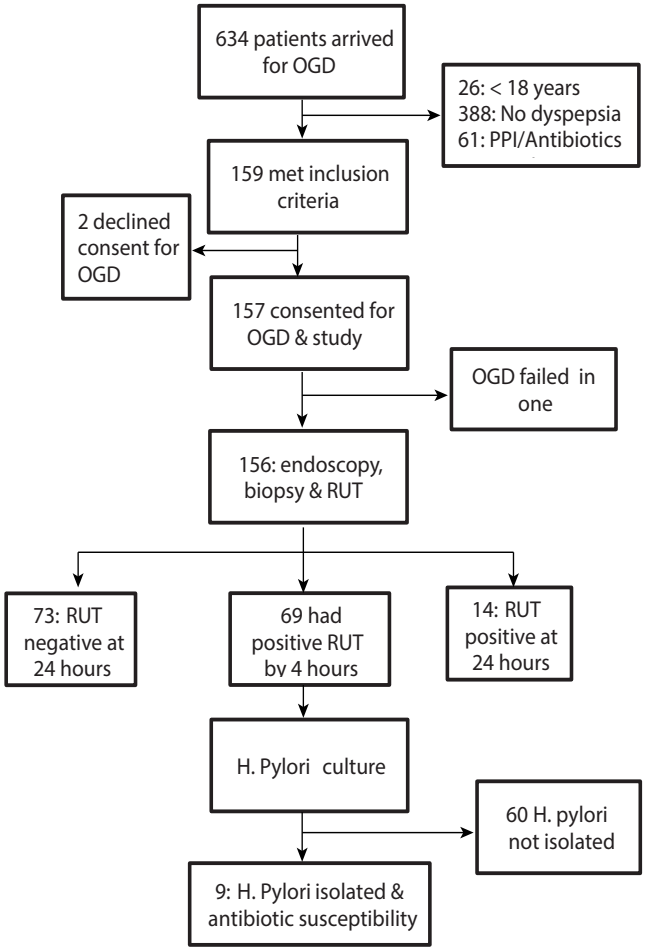
The study received partial funding from AstraZeneca and National Commission for Science Technology and Innovation (NACOSTI), but they played no role in the study design, execution, and data analysis and presentation of results.

This study was approved by Institutional Review and Ethics Committee (IREC), (Formal Approval Number: FAN: IREC 1048) and Moi Teaching and Referral Hospital management.

Results

Between April 2014 and February 2015, 634 patients presenting at the MTRH endoscopy unit for upper gastrointestinal endoscopy were screened of whom 156 were recruited into the study. The rest were excluded for various reasons as shown in Figure 1.

Figure 1: Enrolment schema



The 156 participants enrolled in the study were aged between 18 and 86 years with a median age of 41 (IQR: 28-58) years. Sixty four (41%) were male (Table 1).

Table 1: Demographic characteristics (n=156)

Characteristic	Frequency n (%)
Gender	
Male	64 (41%)
Female	92 (59%)
Age (years)	
18-24	25 (16%)
25-34	34 (22%)
35-44	32 (21%)
45-54	22 (14%)
55-64	20 (13%)
65-74	13 (8%)
>74	10 (6%)

Epigastric pain was the commonest symptom being reported by 151 (97%) of the participants followed by 37 (24%) who reported to have had postprandial fullness as the reason for OGD. Early satiety was not a common symptom of dyspepsia, being reported by only 18 (12%) of participants (Table 2).

Table 2: Clinical characteristics (n=156)

Characteristic	Frequency n (%)
Indications for endoscopy	
Epigastric pains	151 (97%)
Postprandial fullness	37 (24%)
Early satiety	18 (12%)
Dysphagia	4 (3%)
Previous treatment of upper GI disease	
Amoxicillin+Bismuth salt+PPI	2 (1.3%
Amoxicillin+clarithromycin+PPI	1(0.6%)
Amoxicillin+metronidazole+PPI	4 (2.7%)
Amoxicillin+PPI	1 (0.6%)
H2R blocker+PPI	1 (0.6%)
PPI	33 (21.1%)

Thirty three (21.1%) of participants had been treated previously with PPI while 7 had received standard *H. pylor*i eradication treatment (Table 2). The participants received these treatments on average 2.5 months (IQR 2-6) prior to presentation for current OGD and for a median treatment duration of 14 days.

Gastritis was the commonest endoscopic finding in the stomach occurring in 123 (79%) of the participants. Normal stomach was observed in 23 (15%) of the participants. Thirteen (8.3%) of patients had normal upper endoscopic findings. Other findings are as shown in Table 3.

Table 3: Gross endoscopic findings (n=156)

Finding	Frequency n (%)
Gastritis	123 (79%)
Duodenitis	30 (19%)
Oesophagitis	30 (19%)
Normal	13 (8.3%)
Duodenal ulcerations	9 (6%)
Gastric ulcerations	7 (4%)
Hiatus hernia	6 (4%)
Gastric atrophy	3 (2%)
Gastric outlet obstruction	2 (1.3%)
Oesophageal candidiasis	2 (1.3%)
Deformed pylorus	2 (1.3%)
Others	5 (3.2%)
Not done	3 (2%)

Eighty three (53%) of participants were positive for *H. pylori* on Rapid Urease Test (RUT). Patients who had postprandial fullness as the reason for endoscopy were more likely to be RUT positive as were patients who had duodenitis; p values 0.0449 and 0.0041 respectively (Table 4).

Table 4: Association between clinical characteristics and rapid urease test

Clinical characteristic	Frequency (n =156)	RUT positive (n=83)	RUT negative (n=73)	P-value
Epigastric pains	151 (97%)	80 (96.4%)	71 (97.3%)	1[f]
Postprandial fullness	37 (24%)	25 (30.1%)	12 (16.4%)	0.0449[c]
Early satiety	18 (12%)	11 (13.3%)	7 (9.6%)	0.4747[c]
Previous treatment	42 (26.9%)	23 (27.7%)	19 (26.0%)	0.8130[c]
Normal	13 (8.3%)	6 (7.2%)	7 (9.6%)	0.5946[c]
Oesophagitis	30 (19%)	12 (14.5%)	18 (24.7%)	0.1067[c]
Gastritis	123(79%)	67 (80.7%)	56 (76.7%)	0.5405[c]
Gastric ulcerations	7 (4%)	4 (4.8%)	3 (4.1%)	1[f]
Duodenitis	30 (19%)	23 (27.7%)	7 (9.6%)	0.0041[c]
Duodenal ulcerations	9 (6%)	6 (7.2%)	3 (4.1%)	0.5033[f]

[f] = Fischers exact [c] = Chi square test

Sixty nine samples that were positive for *H. pylori* within 4 hours on RUT were cultured. Culture yield was found in 9 (13%) of the samples.

Table 5: Association between clinical characteristics and culture rate

Clinical characteristic	Frequency (n =69)	Culture positive (n=9)	Culture negative (n=60)	P-value (Fischer exact test)
Epigastric pains	68 (98.6%)	9 (100%)	59 (98.3%)	1
Postprandial fullness	21 (30.4%)	1 (11.1%)	20 (33.3%)	0.2583
Early satiety	7 (10.1%)	2 (22.2%)	5 (8.3%)	0.2244
Previous treatment	20 (29.0%)	3 (33.3%)	17 (28.3%)	0.7120
Normal	4 (5.8%)	0 (0%)	4 (6.7%)	1
Oesophagitis	10 (14.4%)	2 (22.2%)	8 (13.3%)	0.6087
Gastritis	57 (82.6%)	9 (100%)	48 (80%)	0.3422
Gastric ulcerations	3 (4.3%)	0 (0%)	3 (33.3%)	1
Duodenitis	19 (27.5%)	4 (5.8%)	15 (25%)	0.2469
Duodenal Ulcerations	5 (7.2%)	0 (0%)	5 (8.3%)	1

There was no significant association between any patient characteristic (including demographics, patients' symptoms, endoscopic findings) and culture rate (Table 5).

There were no strains resistant to clarithromycin. Six (67%) samples were sensitive to amoxicillin while all the 9 strains were resistant to metronidazole. Two thirds of the strains were sensitive to tetracycline while a third were resistant (Table 6).

Table 6: Antibiotic resistance

Antibiotic	Sample size	Susceptibility level	n (%)
Clarithromycin		Sensitive	5 (56%)
	9	Intermediate	4 (44%)
		Resistant	0
Amoxicillin		Sensitive	6 (67%)
	9	Intermediate	1 (11%)
		Resistant	2 (22%)
Metronidazole		Sensitive	0
	9	Intermediate	0
		Resistant	9 (100%)
Tetracycline		Sensitive	6 (67%)
	9	Intermediate	0
		Resistant	3 (33%)

Discussion

Using the Rapid Urease Test (RUT), more than half (53.2%) of patients with dyspepsia undergoing endoscopy at MTRH were infected with *H. pylori*. Our findings were comparable to a previous study by Mwogi (15) in 2010 in the same setting that found a prevalence of 52.3% among adults patients undergoing endoscopy for dyspepsia, as well as another study by Kimang'a *et al* (10) study at Aga Khan University Hospital Nairobi in 2010 that found a prevalence of 54.8%. However, earlier Kenyan studies showed higher prevalence of *H. pylori* among patients with dyspepsia. Lule *et al* (16) in 1991 found a prevalence of 70% among dyspeptic patients. This indicates a general trend of decline of *H. pylori* prevalence among patients with dyspepsia. We attributed this improvement of socioeconomic status in Kenya as well as introduction of triple therapy eradication regimens in the country.

In our study we found *H. pylori* culture rate of 13% following a 24 hour transportation time of the samples to a central laboratory. Several factors could have contributed to the low culture rate observed in this study: first, 28% of the patients had previously been treated for dyspepsia with PPI, H2R blockers and/or antibiotics; second, patients who were not on any medications for up to only two weeks prior to enrolment as opposed to longer duration reducing the isolation rates due to coccoid forms the bacteria assume when exposed to acid suppression and antibiotics (17). The culture rate of 13% was much lower than several other studies. In a study by Veenendaal *et al* (9) in the Netherlands in 1993 in which culture was done after 24 hour delay as in this study, the culture rate was high at 84.6% while in another study by Hachem *et al* (12) in which culture was done 2 to 7 days after sample collection on BHIA as in our study the culture rate was 96%. However there are several differences in methodology between the two studies that could account for the disparity of culture rate with our study. First, while we excluded patients who were on antibiotics within the two weeks of presentation for OGD, Veenendaal *et al* (9) excluded patients who were on antibiotics within three months before presentation. Recent antibiotic and anti-gastric acid secretory drugs reduces yield of *H. pylori* cultures (18). Secondly, Veenendaal *et al* (9) used two antral biopsy specimens while we used one each from the antrum and corpus. This difference in specimen sampling could determine the difference in culture rate as most of the *H. pylori* is known to reside more in the gastric antrum than the corpus (8). Thirdly, our study used 1ml of normal saline as transport media while Veenendaal *et al* (9) used 0.2ml of normal saline. In Hachem *et al* (12) study, Cysteine Albimi media was used as transport media instead of normal saline. The larger volume in transport media in our study could have caused dilution of organisms resulting in low culture rate (19). Fourth, in Hachem *et al* (12) study, incubation was done up to 14 days while in our study culture was done for up to 7 days. Longer incubation periods have been shown to increase the isolation rate (8). Furthermore Veenendaal *et al* (9) study was done several years back (1993) before the widespread use *H. pylori* eradication regimes, which could have an effect on culture rate.

Lule *et al* (16) in a study done locally in Kenya found a culture rate of 70% in 1991, while Lwai-Lume *et al* (19) cultured 69% in 2004 and Kimang'a *et al* (10) isolated 92.3% in 2010. The major difference

between these studies and ours is that for all of them culture was done within 6 hours of sample collection which is expectedly supposed to give a better yield. Furthermore in Lwai-Lume *et al's* (19) study, patients on antibiotics, PPI and H2R blockers within 3 months before culture were excluded.

None of the *H. pylori* isolated in our study were resistant to clarithromycin. This finding is consistent with findings by Lwai-Lume *et al* (19) in 2004 that found only 6.4% of *H. pylori* were resistant and another study by Kimang'a *et al* (10) that found no clarithromycin resistant *H. pylori* among patients with dyspepsia at Aga Khan University Hospital Nairobi. These findings indicate that *H. pylori* in Kenya is still largely sensitive to clarithromycin.

The minority, 2 (22%), of isolated *H. pylori* were resistant to amoxicillin. This findings support previous studies that showed that *H. pylori* has not developed significant resistance to amoxicillin. Lwai-Lume *et al* (19) in 2004 found only 4.6% of *H. pylori* being resistant to amoxicillin while Kimang'a *et al* (10) in 2010 did not find any *H. pylori* strains resistant to amoxicillin. In these two studies, a higher MIC cut of 2mg/l was used to determine the level above which resistance was defined compared to our study that used the MIC cut off of 1mg/l as currently recommended by the Clinical Laboratory Standards Institute (CLSI) (13). The lower cut off in our study could account for a higher resistance in our study.

All *H. pylori* strains isolated in our study were resistant to metronidazole. This antibiotic is widely used for diarrhoeal and other conditions where it's often not indicated and this could explain the total resistance by *H. pylori* (20). Resistance of metronidazole is widespread with 10-50% resistance in developed countries and almost all strains in developing countries (21). Our findings on metronidazole resistance were similar to those reported by Lwai-Lume *et al* (19) in 2004 in which all *H. pylori* were resistant and another by Kimang'a *et al* (10) in 2010 in which 95.4% were resistant. However in another study by Sang *et al* (22) in 1991, no strains of *H. pylori* resistant to metronidazole were found. Sang *et al* (22) study was done more than two decades ago probably before widespread use of antibiotics, the use of which raises the incidence of antibiotic resistance (23).

Thirty three percent of *H. pylori* isolated were resistant to tetracycline. Our findings were higher than previous studies done locally in Kenya. Sang *et al* (22) in 1991 did not isolate any *H. pylori* resistant to tetracycline while Lwai-Lume *et al* (19) in 2004 found only 7.9% of *H. pylori* were resistant to tetracycline. These studies were done more than a decade ago and we postulate that since tetracycline was not part of *H. pylori* eradication regimes frequently used in Kenya, there was less resistance than when compared to our recent study. Our small sample size also has the possibility of exaggerating the proportions.

Study limitations

The culture isolation rates was too low to give a robust recommendation on recommendation for specific antibiotic for *H. pylori* eradication.

Conclusions and recommendations

Over half of the patients with dyspepsia undergoing OGD at MTRH are infected with *H. pylori*. The culture rate of *H. pylori* following 20 to 24-hour transportation time of samples to a central laboratory using normal saline as transport media is low. There were almost no resistant strains of *H. pylori* to clarithromycin while a few strains are resistant to amoxicillin and tetracycline. All *H. pylori* strains isolated were resistant to metronidazole.

We recommend patients with dyspepsia to be tested for *H. pylori* infection as advised by most guidelines. Culture of *H. pylori* after 20-24 hour transportation in normal saline is not useful. A comparative study to determine the optimal transportation time and transport media is recommended. Clarithromycin based therapies without metronidazole is appropriate for *H. pylori* eradication regimens although a larger study on sensitivity patterns is recommended to validate these findings.

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Original paper

Assessment of Characteristics of Patients with Pregnancy related Acute Kidney Injury in Kenyatta National Hospital

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Abstract

Background: Pregnancy Related Acute Kidney Injury (PRAKI) remains a grave complication of pregnancy that is poorly understood. There is paucity of data on patient characteristics. Studies done are few and demonstrate great variability in risk factors and outcome across socio economic boundaries.

Objective: To determine the demographic and clinical characteristics of patients with PRAKI at Kenyatta National Hospital (KNH).

Methods: A descriptive study was carried on pregnant women with gestation age of 28 weeks and above and postpartum women within six weeks after delivery admitted in labour ward or the post natal wards at KNH. Study commenced after approval by the KNH-University of Nairobi Ethics and Research Committee. Follow up was until discharge or for a maximum of two weeks. Patient management was at the discretion of attending clinician.

Results: A total of 66 participants out of 2,068 admissions were enrolled into the study. The prevalence of PRAKI was 3.2%. The mean age was 28 years, with peak age between 26-30 years. Forty two (63.6%) were referrals, of whom 24 (57.1%) were from the rural areas and 18 (42.9%) were from health facilities within the City of Nairobi. Nineteen (27.8%) participants had premorbid medical conditions of which cardiovascular diseases, 16 (24.2%) were the majority. All participants developed single or overlapping obstetric complications of which, predominantly: preeclampsia 28 (42.4%), eclampsia 8 (9.1%) and Haemolysis with Elevated Liver Enzyme Low Platelet (HELLP) syndrome 17 (25.8%). Noted with volume loss were 9 (13.6%). Average gestation age at delivery was 35 weeks. Preterm births were 33 (55%) and fresh still births were 17 (25.8%). There was a six fold increase in fresh still births among participants. Severity of PRAKI at presentation was evenly distributed across stages 1 to 111. Nineteen (28.8%) participants were treated with haemodialysis. The rest were managed conservatively. There was no maternal mortality reported during the study period.

Conclusion and recommendations: The study demonstrated that the majority 63.6% of the participants were referrals mainly from the rural areas. Hypertensive disorders of pregnancy were the main predisposing factors to PRAKI. Most, 55% of the infants were born prematurely of whom 43.5% were fresh still births. Kenyatta National Hospital is a referral facility and the findings of this study may not be representative of the actual patient characteristics in Kenya. Therefore, future studies should aim at multicenter approach to unveil disease burden and patient characteristics across the country.

Key words: PRAKI, KNH, Kenya, Preterm birth, Fresh still birth

Introduction

Pregnancy Related Acute Kidney Injury (PRAKI) is a rare obstetric complication that is poorly understood, characterized by rapid deterioration of renal functions within hours to days, in pregnancy or in the postpartum period, in otherwise healthy women. It is often associated with significant maternal and foetal morbidity and mortality (1,2).

Patient characteristics vary widely due to differences in demographics, comorbid disease burden and quality of healthcare services (3). In the developed world, PRAKI contributes 0-1% of all the Acute Kidney Injury (AKI) in the general population, while in the developing world, PRAKI contributes between 5-20% (4,5). Recent studies demonstrate rising trends in the incidence of AKI in the general population and a paradoxical rise in the incidence of PRAKI in developed world which is attributable to increase in lifestyle diseases, mainly, hypertension and diabetes mellitus and rising maternal age due to advances in reproductive services (4). The aetiologies of PRAKI are similar to those in general population.

Due to the renal and systemic adaptations in pregnancy, small derangement in serum creatinine in pregnancy may be associated with profound kidney injury. Diagnosis of PRAKI is based on combination of clinical and laboratory parameters (1-5).

The principles of management of PRAKI involve risk identification and modification, supportive care and renal replacement therapy (4-8).

Materials and methods

Study design: This was a descriptive study.

Study site: The study was carried out in KNH in the Department of Obstetrics and Gynaecology, in the labour ward and post-natal wards.

Study population: The target population consisted of pregnant women with gestation age of 28 weeks and above and postpartum women within six weeks after delivery admitted at labour ward or the post natal wards of KNH.

Inclusion criteria: Pregnant women with gestation of ≥28 weeks and postpartum women within six weeks with a diagnosis of acute kidney injury or with deranged serum creatinine meeting the operational definition of PRAKI in any of the stated wards willing to sign consent to be enrolled in the study.

Exclusion criteria: Women with chronic kidney disease, or pregnant <28 weeks or in postpartum greater than six weeks, and those who declined consent to be enrolled in the study.

Sampling method: Consecutive patient sampling, purposive, non-random.

Ethical considerations: The study commenced upon approval by the Ethics and Research Committee of KNH and University of Nairobi. Approval number: P635/11/2017

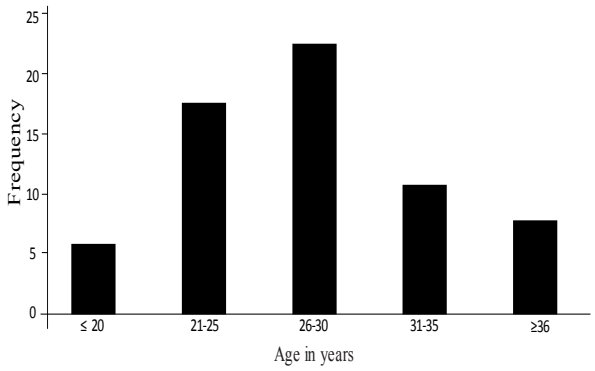
Clinical methods: Patient management was at the discretion of attending clinician. The principal investigator or the research assistant approached each participant and gave detailed verbal explanation of the study requirements:- that there were to be verbal interviews, need for permission to access information from medical file, benefits- interpretation of results were to be communicated to both patient and primary health care provider, risks –that there were to be no risks. The patient was also informed that participation was voluntary and withdrawal from the study was not going to compromise service delivery. Patient's medical records were then assessed and data capture form was used to extract demographic and clinical data.

Data processing and analysis: Raw data was screened, coded and entered into a password protected computer statistical analysis was performed in Statistical Package for Social Sciences (SPSS) version 21.0 by a statistician. Descriptive statistics were used to summarize the findings where continuous variables were described in means or median and categorical variables were summarized into frequencies. Other statistical test results were presented in tables.

Results

A total of 66 (3.2%) participants were enrolled out of 2068 admissions during the study period. The mean age was 28 (SD5.9) years with peak age between 26-30 years (34.8%). Age range was 15 to 44 years. In extremes of age, were, below 20 years six (9.1%) and above 35 years, eight (12.12%).

Figure 1: Age distribution of participants with PRAKI



Forty one (62.1%) lived in urban (Nairobi) setting of whom 18 (43.9%) were referred from health facilities within Nairobi while 25 (37.9%) lived in the rural areas out of whom 24 (96.0%) were referrals.

Table 1: Residence distribution among participants with PRAKI

Residence	No.	(%)
Urban (Nairobi)	41	62.1
Rural	25	37.9
Referred n=42 (63.6%)		
Rural	24	57.1
Urban	18	42.9

Nineteen (28.8%) had premorbid conditions which were predominantly cardiovascular diseases and three (4.5%) had human immunodeficiency virus infection.

Table 2: Premorbid conditions among patients with PRAKI

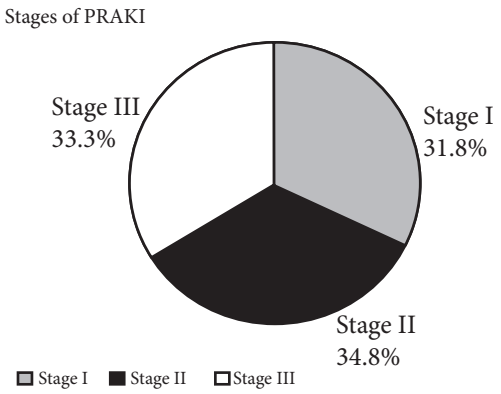
Premorbid (n=19), 28.8%	No.
Hypertension	10
Cardiac disease	6
Valvular heart disease (n=4)	
Dilated cardiomyopathy (n=2)	
HIV	3

Hypertensive disorders:-preeclampsia, eclampsia and HELLP syndrome were the predominant risk factors in 53 (80.3%) participants of whom, 18 (34.0%) had history of gestational hypertension. Nine (9.1%) suffered volume losses which was mainly due to obstetric causes while sepsis and injuries accounted for two (3%) each.

Table 3: Morbid /obstetric conditions among patients with PRAKI

Morbid (n=66)			No.
Hypertensive disorders			53
	No.	(%)	
PET	28	52.8	
Eclampsia	8	15.1	
HELLP	17	32.1	
Volume loss			9
Puerperal sepsis			2
Injuries (bladder, urethral)			2

Figure 2: Distribution of severity of PRAKI at presentation



A total of 60 pregnancies were delivered and six were ongoing as at the end of follow up period. Majority were delivered through Caesarian section of which 85.7% were emergency deliveries. No maternal mortality was reported during the follow-up period.

Table 4: Maternal and pregnancy outcome in PRAKI

Outcome	No.	(%)
Pregnancy status Ongoing	6	9.1
Delivered	60	90.9
Mode of delivery (n=60)		
SVD	39	59.1
CS	21	31.8
Need for CS Emergency CS	18	85.7
Elective	3	14.3

The average gestation age at birth was 35 weeks. Thirty-three (55%) were preterm infants. Fresh still births were 17 (28.3%) of whom, 10 (58.8%) were preterm births. There was a six fold increase in fresh still births among the patients with PRAKI.

Table 5: Foetal outcome in PRAKI

	Foetal status at birth (n=60)				
Age at birth	Live infant (n= 43)		Fresh still birth (n=17)		Total (%)
	No.	(%)	No.	(%)	
Preterm< 37 weeks	23	(53.5)	10	(58.8)	33 (55.0)
Term >37 weeks	20	(46.5)	7	(41.2)	27 (45.0)
Total	43	(71.7)	17	(28.3)	60 (100)

Majority (48%) of those who worsened were in stage 111 at presentation.

Table 6: Trends of serum creatinine of PRAKI

	Stage of PRAKI			
Trends of serum creatinine	Stage 1	Stage 2	Stage 3	Total
Improved	16 (39.0)	15 (36.6%)	10 (24.4%)	41
Worsened	5 (20.0%)	8 (32.0%)	12 (48.0%)	25

Nineteen (28.8%) were dialyzed, while 47 (72.2%) were managed conservatively.

Table 7: Need for dialysis in PRAKI

	Stage of PRAKI			
	Stage 1	Stage 2	Stage 3	Total
Need for dialysis	2 (10.5%)	3 (15.8%)	14 (73.7%)	19
No need for dialysis	19 (40.4%)	20 (42.6%)	8 (17.0%)	47

Discussion

The study demonstrated peak age of 26 to 30 years, which was similar to peak age reported in many studies in the developing world (3,4) and lower than peak age of 30-39 years in Canada. This age difference may be due to availability of advanced reproductive technology in the developed world, where facilitated conception in older women is possible (4).

In our study, the prevalence of PRAKI was 3.2%, this was higher than that reported in India by Prakash *et al*. (5), where PRAKI complicated 1 in 56 viable pregnancies with a prevalence of 1.78% and in Morocco where PRAKI was reported in 1 in 151.5 deliveries, with a prevalence of 0.66% (7), however, our prevalence was lower than in Malawi where PRAKI complicated 1 in 12.3 pregnancies with prevalence of 8.1% (9). The high prevalence in our setting might have been due to the high numbers of referred patients.

Hypertensive disorders were found to be the main predisposing factors to PRAKI whereas obstetric haemorrhage occurred in 7 (10.6%) of participants. These findings are similar to those from other developing countries such as Morocco 9.1% (7) and lower than 17.6% in Canada (4). The difference in these findings may be due to differences in quality of care and maternal characteristics.

Concomitant with the decrease in the incidence of PRAKI, maternal mortality associated with PRAKI has significantly decreased worldwide (4-8). Recent studies from China and India reported maternal mortality rate of 4.0% and 5.8%, respectively down from 20% in the 1980s (8). In this study, no maternal mortalities were documented over the study period. This finding compares with those of a study done in Malawi by Cooke *et al*. (9) where no maternal mortality was documented in a similar study setting. This finding contrast findings in studies done in Morocco and India where maternal mortality was 11.4% and 15% respectively (7,10). Findings of this study and that in Malawi may reflect a declining maternal mortality in developing countries but do not necessarily mean that there are no maternal mortalities associated with PRAKI .

Pregnancy related acute kidney injury is associated with increased operational deliveries and foetal loss (3,6). We found the ratio between CS in PRAKI to CS in non PRAKI patients was 1.4:1. The increase in operational delivery may be explained by the fact that, delivery of the foetus and the placenta is therapeutic in hypertensive disorders of pregnancy (5,8) which as explained earlier are the most common aetiologies of PRAKI. This may also explain why premature deliveries were noted to be higher than term deliveries at a ratio of 1.2:1 in our study.

We documented 17 (28.3%) fresh still births which was higher than 11.7% reported by Kabbali *et al* (7) in Morocco and lower than 41% reported by Munna *et al* (10) in India and unlike the findings by Hildebrand *et al* (4) in Canada where no still births were reported. These findings may reflect differences in antenatal and perinatal care practices and also the challenges in handling non obstetric emergencies like acute kidney injury in resource strained setting. The ratio of fresh still births among the study participants was 1:4 which was much higher than 1:23 in patients without PRAKI during the study period. Therefore, PRAKI increased the risk of fresh still birth by six fold. This finding was higher than that documented by Liu *et al* (11) from meta analyses where PRAKI was documented to cause a 4.9 fold increase in fresh still births. The high rate of fresh still births in our setting may be due to late referrals, high patient turnover and strained resources.

The long term renal outcome could not be ascertained in this study due to the short follow up period. However, 41 (62.1%) improved on conservative management while 25 (37.9%) worsened, of whom 19 (28.8%) required renal replacement therapy which was mainly due to fluid overload 63.2%. The need for haemodialysis was higher than 16.2% documented by Cooke *et al.*(9) in Malawi and lower than in a study in Morocco by Kabbali *et al*. (7) in 2010 and India by Prakash *et al*. (5) ,where the need for dialysis was 38.6% and 54.6% respectively. These findings may reflect the variability in the supportive measures in different settings.

Conclusion

The prevalence of PRAKI from this study at KNH is 3.2%. The main risk factors were hypertensive disorders of pregnancy. There was six fold increases in fresh still births among patients with PRAKI.

Recommendations

There is need for a multicenter study in Kenya in a non-referral setting to determine actual disease burden and patient characteristics.

Acknowledgements

To my supervisors, lecturers, and colleagues in the Department of Clinical Medicine and Therapeutics for their support.

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Original paper

Prevalence of Urinary Tract Infections among Kidney Transplant Recipients in Kenyatta National Hospital, Kenya

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Abstract

Background: Urinary Tract Infections (UTIs) form the largest percentage of post kidney transplantation infections. These UTIs are more likely to be clinically asymptomatic and more aggressive compared to non-transplant population. The prevalence and microbial patterns vary between centers. There is no known local data describing prevalence and patterns in our set up.

Objective: The aim of the study was to determine the prevalence of bacterial and fungal urinary tract infections and their clinical and microbiologic patterns among kidney transplant recipients in Kenyatta National Hospital (KNH).

Design: Cross sectional descriptive study.

Methodology: The study population was kidney recipients aged 18 years and above, attending follow up clinic at KNH. A total of 99 patients were recruited between November 2013 and March 2014 via consecutive sampling. Presence of UTI was assessed by collection of mid-stream sterile urine that was analyzed by urinalysis, microscopy and culture and sensitivity.

Results: Twenty one percent of participants had UTI. Females were affected more than men, 38.5% and 15% respectively. Eighty six percent of the UTIs were asymptomatic. Twelve percent of UTI were culture positive. Gram negative bacteria were the commonest, with *E. coli* making the highest percentage (58%). Forty percent of Gram negative bacilli were ESBL positive.

Conclusion: The prevalence of UTI in our population was high with a prevalence of 21%. The majority of the UTIs were asymptomatic and involved a higher percentage of females. Gram negative bacteria were the majority with *Escherichia coli* being the most isolated. Emergence of extended spectrum beta lactamase bacteria was a matter of grave concern noted.

Key words: Urinary tract infections, Kidney transplant recipients, *Escherichia coli*

Introduction

Worldwide, the number of individuals receiving Renal Replacement Therapy (RRT) is estimated at more than 2.5 million (1) with incidence growing by approximately 8% annually (2). Compared to dialysis renal transplantation is superior and makes about 30% of patients on RRT (3). Kidney rejection and infections are the greatest hindrances to success of allograft organ transplantation (1).

Renal transplant recipients develop Urinary Tract Infections (UTIs) more frequently than the general population (4). UTI is the most common infection following renal transplantation, accounting for approximately 44–47% of the infectious complications (5,6). The reported incidence of post-transplantation UTI varies considerably with study design, local outbreaks, definition and diagnostic criteria (5-9). Despite improved immunosuppressive and antimicrobial therapy UTIs continue to be a major problem (5, 9).

Organisms that cause UTI after renal transplantation can be bacterial, fungal, viral, parasitic or mycobacterial (6,9). Bacterial causes account for the highest portion of the organisms even up to 97% (7,9). The hierarchy of bacterial UTI pathogens in transplant recipients is similar to that in the non-transplantation population, with Gram negative bacterial infections accounting for more than 70% of UTIs. *Escherichia coli, Enterococcus sp.* and *Enterobacter cloacae* are the most common enteric organisms that cause UTI in transplant recipients. Other less common bacterial causes are *Pseudomonas*, *Klebsiella* and *Proteus mirabilis*. Low-virulence bacteria that would not be pathogenic in immunocompetent hosts have been implicated in post-transplantation UTI.

Renal recipients with UTIs are more likely to be clinically asymptomatic compared to non-

immunocompromised patients, and do not mount the typical inflammatory response to infection as a consequence of immunosuppressive therapy. UTI in this group is often associated with acute pyelonephritis and rapidly developing bacteraemia potentially progressing to the full-blown picture of urosepsis, particularly during the early post-transplant period. Patients are at especially high risk for UTI in the first month post-transplant. In a study by Chuang *et al* (8) nine of the ten patients who died from sepsis had post-transplant UTIs. Wegener *et al* (10) while investigating commonest cause of bacteremia in kidney transplant recipients, UTI was the commonest source.

Kidney recipients are usually on prophylactic antibiotic mainly cotrimoxazole and receive frequent empirical antibiotic treatment due to recurrent episodes of infection, both urinary and non- urinary related. This may alter presentation of UTIs in post-transplant recipients and their likely microbial sensitivity patterns.

There is no known local published data on prevalence of UTIs or microbiological patterns on this group of patients. The study aimed to determine the prevalence of urinary tract infections and their clinical and microbiologic patterns among kidney transplant recipients in our setup. We sought to examine bacterial and fungal infections in a predominantly living related donor renal transplant recipients.

Materials and methods

Study subjects: This was a cross sectional study conducted from November 2013 to March 2014 on Kidney Transplant Recipients (KTRs) attending the renal transplant clinic at Kenyatta National Hospital (KNH). KNH is a state owned national referral and teaching hospital, situated in Nairobi, Kenya. KNH is among the only three hospitals performing kidney transplants in Kenya and the only public hospital. It runs a robust transplantation program with a weekly follow up clinic, whereby the recipients attend on appointment or if need arises.

The study included all KTRs aged 18 years and above, who consented to the study and had been transplanted more than a week prior to the study. The minimal sample size of 98 was calculated using an estimated prevalence of 29.5% from a Libyan population (11), with a living donor (predominantly related) kind of population of KTRs.

Consecutive sampling was done and 107 KTRs were screened. Eight KTRs were excluded and 99 participants were recruited. Socio-demographics data was collected including age, gender and level of education. Further details were retrieved from the file and pre-transplant check list, including cause of ESRD, how long the patient had dialysed before transplant, date when the transplantation was done, current immunosuppresives and their doses.

Evidence of prior UTI was assessed in the file using the study criteria for UTI. Clinical history and physical examination was carried out with emphasis on the urinary system. The history focused on the symptomatology of the UTI i.e. frequency, dysuria, urgency and usage of antibiotics one month prior. Abdominal exam was done focusing on suprapubic, graft and renal angle tenderness.

Ten ml of clean catch mid-stream urine was obtained in a sterile container from all the participants. Urinalysis, microscopy and culture was done for all recruited. Standard Operating Procedures (SOPs) for microscopy and culture growth were followed. Microscopy of uncetrifuged urine was carried out in a neubar chamber. Analysis for nitrites and leucocyte esterase was then conducted. Then 0.001ml loop was used to plate specimens for culture on blood agar, MacConkey's agar and Cysteine Lactose Electrolyte Deficient (CLED) media. Incubation was done for 24 hours at 35°C–37°C in ambient air before being read. Identification of the organisms was carried out when growth was observed. Antimicrobial sensitivity was done for each organism depending on standard set of antibiotics tested against it as per CLSI guidelines. Most pathogenic yeasts grow well on blood agar plates; therefore no selective fungal media for cultures was used.

UTI case definition

A UTI is diagnosed based upon any one of the following:

(i) Pyuria ≥10 WBC/ml of uncentrifuged urine
(ii) Urinary leukocyte esterase positive
(iii) Nitrites positivity
(iv) Positive urine culture ≥ 10^5 CFU/ml

Each case was defined as either symptomatic or asymptomatic. Symptomatic was defined as the presence of any of the following: frequency, dysuria, urgency, temp >38.3°C, tenderness over suprapubic, renal angle or over the graft. Asymptomatic was absence of any above features. All those who tested positive were informed of the results and referred to the physician attending the patients in the clinic for further care.

The Department of Clinical Medicine and Therapeutics, University of Nairobi and the Kenyatta National Hospital/University of Nairobi Research and Ethics Board (KNH/UON-REC) approved this study.

Statistical analysis: Statistical analysis was performed using SPSS version 18.0. Continuous data i.e. age, duration of dialysis and time after transplantation was summarized into means, standard deviation,

modes, median, and range. Categorical data e.g. gender, education, immunosuppressive therapy was summarized into proportions and percentage. Prevalence was calculated as percentage of the whole study sample. Results were presented as tables, bar charts, line graphs and pie charts.

Results

The socio-demographic and clinical characteristics of the study participants are summarized in Table 1.

Table 1: Socio-demographic and clinical characteristics among kidney recipients (N=99)

Characteristic		Value
Age in years		
	Mean, SD	42.5 ±13.4
	Min-Max	18-72
Male (%)		73 (73.7)
Number with post primary education (%)		84 (84.8)
Cause of ESRD (%)		
Chronic Glomerulonephritis		49 (49.5)
Diabetes Mellitus		20 (20.2)
Systemic hypertension		19 (19.2)
Bladder Outlet Obstruction		3 (3.0)
Polycystic kidney disease		3 (3.0)
Other		5 (5.2)
Duration of dialysis in months		
Mean		22.7 ±22.6
Min-Max		0-156
Average time since transplantation in months		
Mean		33.5±48
Min-Max		0.3-268
Number of kidney transplantation (s) (%)		
One		98 (98.9)
Two		1 (1.0)
Current immunosuppressive therapy (%)		
Prednis+Mycophonolate+Ciclosporine		51(51.5)
Predn+Mycophenol+ Tacrolimus		43 (43.4)
Prednisolone+Azathioprine		5 (5.1)
Number on Cotrimoxazole prophylaxis (%)		15(15.2)
Number with antibiotic use one month prior		20(20.2)
Prevalence of UTI		21(21.2)

Twenty one (21.2%) participants had UTI. Males were 11 and females 10. This then translates into 15% and 38.5% of all (n=99) males and females respectively. Eighty six percent were asymptomatic. Their clinical characteristics are summarised in Table 2.

Table 2: Clinical characteristics for kidney recipients with UTI (N=21)

Characteristic		Value
Age in years		
	Mean, SD	41.8 ±15.5
	Min-Max	18-72
Number of male (%)		11 (52.4)
Cause of ESRD (%)		
Chronic Glomerulonephritis		13 (61.9)
Diabetes Mellitus		4 (19.0)
Systemic hypertension		2 (9.5)
Bladder Outlet Obstruction		1 (4.8)
HIV		1 (4.8)
Duration of dialysis in months		
Mean		22.7±22.6
Min-Max		3-156
Average time since transplantation in months		
Mean		38.4±48
Min-Max		1-170
Number of kidney transplantation (%)		
1		20 (95.2)
2		1 (4.8)
Current immunosuppressive therapy (%)		
Prednisol+Mycophonola+Ciclosporine		10 (47.6)
Prednisol+Mycophenola+ Tacrolimus		10 (47.6)
Prednisolone+Azathioprine		1 (4.8)
Number with symptomatic UTI[a] (%)		3 (14.3)
Number on Cotrimoxazole prophylaxis (%)		6 (28.6)
Number who used antibiotic one month prior[b] (%)		3(14.3)

a: Symptomatic UTI= History: (frequency /dysuria / urgency) or Exam (Temp ≥38.3°C/ Tender suprapubic/ Tender renal angle/ Tender area over graft)
b: all had used ciprofloxacin

Seventeen patients had positive cultures specimens. Five did not meet the colony threshold of 100000(10^5) CFU/ml. and were excluded from analysis. Out of the twelve remaining growths, one grew fungal and the rest were bacterial in origin. These were *Escherichia coli, Klebsiella pneumoniae, Enterococcus spp, Citrobacter koseri, Proteus vulgaris and Candida spp.* Fifty eight percent were *E. coli* while each of the rest organism was 8%.

Antimicrobial sensitivity according to CLSI guidelines was done to all significant cultures except for the fungal isolation. Sensitivity was done for fifteen antimicrobials and this is depicted in Tables 3 and 4.

Table 3: Antimicrobial sensitivity among kidney recipients, in percentage (n=11)

Organism	N	TMP-SMX		Ciproflo		Amox-Clav		Ceftriax-one		Cefotaxime		Ampiclox		Gentamycin	
		S	R	S	R	S	R	S	R	S	R	S	R	S	R
E. coli	7	0	100	14	86	57	43	57	43	57	43	0	100	29	71
Proteus	1	0	100	100	0	100	0	100	0	100	0	0	100	100	0
Klebsiella	1	0	100	0	100	0	100	0	100	0	100	0	100	0	100
Enterococcus	1	N	N	N	N	100	0	N	N	N	N	100	0	N	N
Citrobacter	1	0	100	100	0	0	100	100	0	100	0	0	100	100	0

S=Sensitive; R=Resistant; N=Not tested

Table 4: Antimicrobial sensitivity among kidney recipients, in percentage (n=11)

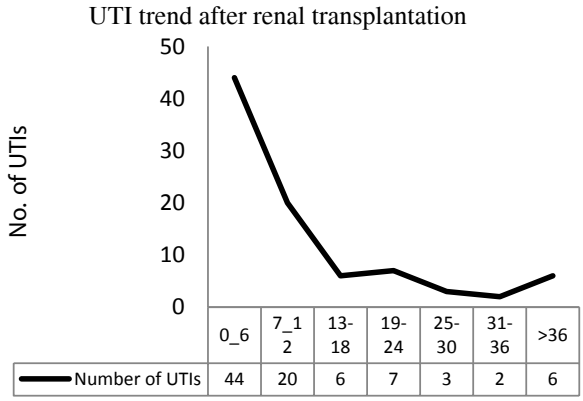
Organism	N	Amikaci		Nitrofurantoin		Cefuroxime		Nalidixic		Tetracyclin		Fosfomyci	
		S	R	S	R	S	R	S	R	S	R	S	R
E. coli	7	100	0	57	43	57	43	14	86	0	100	86	14
Proteus	1	100	0	0	100	100		100	0	0	100		
Klebsiella	1	100	0	0	100	100	0	0	100	100	0		
Enterococcus	1	N	**N**	100	0	N	N	N	N	100	0	100	0
Citrobacter	1	100	0	100	0	100	0	0	100	100		100	0

S=Sensitive; R=Resistant; N=Not tested

None of the bacterial cultures isolated were susceptible to cotrimoxazole. Only 3 (27%) out of 11 were sensitive to ciprofloxacin. Only about half (54.5%) of cultures were sensitive to amoxiclav (6 out of 11). Ceftriaxone had a relatively good (60%) sensitivity of six out of ten cultures tested. Amikacin had the best (100%) antimicrobial activity, however only four out of ten cultures were sensitive to gentamycin (40%). Susceptibility to carbapenems (meropenem, imipinem & ertapenem) was only done to ESBL positive cultures and they were all susceptible.

Review through the participants files revealed occurrence of at least one UTI (Leucocyte Esterase positive or Nitrite positive or culture) in 33 patients (33.3%). Twenty two were males and eleven were females. There were 88 counts of UTIs from the participants' records. Half of the UTIs occurred within the first 6 months of transplantation and 73% within one year. The number reduced with time and was remarkably low by the end of 24 months after transplantation, as shown in Figure 1.

Figure 1: History and trend of UTI among the kidney recipients (n=99)



Discussion

Twenty one participants (21.2%) had a diagnosis of current UTI. This finding is significantly high. Elkehili and Ahmed (11) in Libya found a prevalence of 29.5% in his predominantly living related donor retrospective study and Pourmand and Salem (12) in Iran found 41.5% in a predominantly living unrelated donor prospective study with one year follow up.

Eighty six percent of the UTIs were asymptomatic. This is not unusual as revealed by Maraha and Bonten (7). Underlying diseases such as advanced diabetic neuropathy, combined with denervation of the allograft and immunosuppressive medications, especially corticosteroids, affect the reliability of clinical symptoms.

Eighty four percent of the causative microorganisms were gram negative, similarly observed at 65% and 53% by Chuang *et al* (8) and Elkihili *et al* (11) respectively. *E. coli* made up the majority (58%) of the organisms grown, which is higher than what was shown by Elkihili *et al* (11) (25.8%) and Chuang *et al* (8) (29%) but lower than Senger *et al* (13) (61%).

In the general population *E. coli* causes 80-90% of UTIs. However, in renal transplantation population, despite being the commonest organism isolated, its relative contribution is less, revealing a change in microbiological pattern that has a bigger contribution from other organisms.

While in our study only 8% of culture-positive UTIs were caused by gram positive bacteria, other studies have shown higher relative frequencies, Alangaden *et al* (5), Maraha *et al* (7) and Roberto *et al (14)*, in three separate studies have noted *Enterococcus spp*. as an emerging bacterium with contribution of up to 33%.

Fungal UTI from *Candida spp* made up a relative frequency of 8% and 1% of all the study participants. This matches several others studies (5,8,9). *Candida* UTIs can have serious consequences and may cause ascending infection. Therefore, treatment of *candiduria* (even if asymptomatic) is recommended in renal transplant recipients (4,15).

This study found 100% resistance to trimethoprim/sulfamethoxazole (TMP-SMX). Similar finding was reported by Senger *et al*. (13)TMP/SMX prophylaxis could induce and result in the emergence of resistant species and failure of the employed prophylaxis in preventing UTI development in individual patients.

Seventy percent to the gram negative bacilli were resistant to ciprofloxacin, similarly observed by Senger *et al* (13) at 75%. However, Elkehili and Ahmed (11), in two separate studies, found lower resistance at 48% and 46% respectively. In his work in South Africa, Fredricka *et al* (16) found 11% and 41% resistance to ciprofloxacin in uncomplicated and complicated non transplant UTIs respectively**.** Our population which has complicated UTIs, frequent contact with health facilities, is on immunosuppresives and anatomical abnormalities from transplantation may be predicted to have higher resistance pattern.

Amikacin had the best (100%) antimicrobial activity. Fosfomycin closely *followed* at 89% antimicrobial susceptibility. Despite good antimicrobial cover, amikacin is used with caution due to risk of nephrotoxicity. Fosfomycin is not recommended in complicated UTIs (17). The rare use of these two antibiotics may have preserved them from the high resistance pattern noted with other antibiotics.

Three out of seven *Escherichia coli* isolated were ESBL positive, and the only *Klebsiella pneumoniae* isolated was ESBL positive. This makes 42.9% and 40% of all *E. coli* and gram negative bacilli were ESBL positive respectively. In their work Valera *et al* (9) found that E. ESBLEC made up 24%. Infections caused by ESBL producers are associated with increased mortality, length of stay and increased cost. An inadequate empirical therapy for serious infections caused by these organisms is independently associated with increased mortality (18). Monitoring for ESBL production and antimicrobial susceptibility testing are necessary to avoid treatment failure in management of UTI.

Review through all the participants' files and records revealed a 50% and 73% UTI occurrence in the first six months and one year respectively after transplantation, with a plateau at 24 months. This early post kidney transplant time correlates with the period of the highest immunosuppresion, recent hospitalization and recent injury to tissues during procedures like surgery, urinary catheterization among others. In addition, reactivation of latent or partially treated pre transplant UTIs may contribute to the high prevalence (4). Valera *et al* (9) found 50% of UTI occurred in first 44 days while Elkihili *et al* (11) found 72% of UTI occurred in first 3 months post transplantation emphasizing our observation. UTIs presenting in the first 6 months post transplantation are associated with overt pyelonephritis, bacteremia and high rate of relapse when treated with a conventional course of antibiotics (19). Need for heightened surveillance and high index of suspicion cannot therefore be overemphasized.

Our study had several limitations. This was a cross sectional study therefore reducing the advantage of a study with a follow up period. Absence of routine urine cultures on the transplant recipients on follow up at KNH. If present it would have added more information on the causative microorganisms and antimicrobial sensitivity patterns. This study did not evaluate viral causes of UTI.

Conclusion and recommendations

UTI prevalence in our population was high with a prevalence of 21%. Majority of the UTIs were asymptomatic. A higher percentage of females were involved. Gram negative bacteria caused the majority of UTIs with *Escherichia coli* being the most isolated. Emergence of ESBL bacteria, a matter of grave concern was noted.

Our recommendations include routine urine cultures especially in the first six to twelve months after kidney transplantation for recipients on follow up at KNH at every visit (monthly). This would allow choosing of antimicrobial agent(s) tailored on culture and sensitivity. There is need to develop a dynamic antibiogram that is regularly reviewed by the transplantation team. This would inform a better empirical therapy as the clinicians await culture results. Further studies with longer observation time to evaluate the clinical course of UTIs and graft function and mortality.

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Original paper

An Assessment of the Knowledge and Adherence to the Recommended Intrapartum Protocols of PMTCT of HIV by Health Workers in a Peri-Urban Hospital in Kenya

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Abstract

Background: In Kenya, 37,000-42,000 babies are infected with HIV yearly through Mother-To-Child Transmission (MTCT), with labour and delivery posing the greatest risk for babies (10-20%). Anecdotal reports suggest that poor knowledge of health workers and lack of adherence to intrapartum Prevention of Mother-To-Child Transmission (PMTCT) of HIV protocols might be contributing to MTCT of HIV during labour.

Objectives: To evaluate knowledge on intrapartum protocols of PMTCT of HIV and adherence to recommended protocols by Health Care Workers (HCWs) in a District Hospital in Kenya.

Design: A cross-sectional study was done in a peri-urban district hospital in Nairobi, Kenya.

Methodology: In total, 110 HCWs were recruited, their knowledge on intrapartum methods of PMTCT of HIV tested, and their adherence to the recommended protocols evaluated during labour, delivery, and post-partum. Tests for statistical significance were done using the Chi-square test at 95% CI.

Results: Participants were mostly female (65.5%), 20-24-year-old (50.9%) HCWs with tertiary education (63.6%). Approximately 63.7% of HCWs were clinical officers (25.5%) or nurses (38.2%). Most HCWs (87.3%) were aware of recommended intrapartum protocols for PMTCT of HIV in Kenya. However, only 38.2% of HCWs adhered to the recommended protocols with females HCWs (OR=3.4, p<0.01) and HCWs with training on PMTCT of HIV (OR=2.9, p=0.02) having 3.4 and 2.9 times the odds of adherence than males and poorly trained HCWs.

Conclusions: Knowledge on intrapartum methods of PMTCT of HIV did not translate to a high adherence. Most HIV positive parturients received sub-optimal care during labour and delivery due to lack of training and stationing of unqualified and unsupervised HCWs in the labour wards.

Key words: HIV, Health care workers, PMTCT of HIV, Intrapartum PMTCT of HIV

Introduction

Data from UNAIDS indicates that approximately 36.7 million people globally are infected with HIV. About 5000 new infections are reported daily, mainly in Sub Saharan Africa (SSA) (1). In 2009, 370,000 children were infected with HIV through MTCT during pregnancy, birth, and breastfeeding (2). The incidence of MTCT dropped to 160,000 new cases in 2016 (1) with the incidence in Kenya reported to be about 18% (3), which translated to approximately 37,000- 42,000 new HIV infections in babies. A few cases of MCTC of HIV occur *in utero* with trans-placental transmission of HIV to babies reported in 5-8% of cases. Labour and delivery pose the greatest risk with 10-20% of new infections occurring at this stage (4). Preventing MTCT of HIV intrapartum could help Kenya to achieve its target of reducing its incidence to <5%.

A priority area of the Kenya National AIDS Strategic Plan of 2000-2010 was to eliminate MTCT of HIV. This plan required health workers to adhere to a set of strict clinical and public health standards and a cascade of interventions, which begun with HIV counseling and testing of pregnant mothers at the initiation of antenatal care (ANC). To lower MTCT of HIV further, the plan also proposed provision of antiretroviral drugs (ARVs) during pregnancy in preterm and post-term periods, and modification of routine intrapartum obstetric care during labour and delivery. The widespread use of antiretroviral therapy (ART) and planned Caesarean sections (CS) for HIV positive parturients has led to a reduction in the risk of MTCT of HIV in Kenya (5). However, whether health workers in peri-urban centers of health in Kenya know and follow these recommended intrapartum guidelines for PMTCT of HIV is a matter for speculation.

Materials and methods

Study design: A cross-sectional study was done at Mbagathi District Hospital (MDH) in Nairobi. MDH is a public facility that is managed by the Ministry of Health, Kenya. It has a catchment population of three million and serves as the main district hospital in Nairobi. MDH is located near Kibera slums – a densely populated and under-served informal settlement with poor sanitation, poor waste disposal, high infectious disease burden, and high levels of unemployment. MDH serves approximately 1,000 patients per day with an average of 450 deliveries reported in its 120 bed-capacity maternity wing every month. Herein, the prevalence of HIV among parturients during the first quarter of 2015 was 3.3% to 4.6%. The target population was health workers at MDH who were providing intrapartum care to HIV positive parturients in the hospital's labour ward. Consultant obstetricians, gynaecologists, Medical Officers (MOs), medical officers on internship, clinical officers, midwives, and nurses on attachment at the MDH labour ward were targeted.

Data collection: Three tools were used for data collection. After attaining written informed consent, a structured questionnaire was used to capture the socio-demographic data of health workers and to test their knowledge on the obstetric protocols for PMTCT of HIV. After the completion of interviews, a structured checklist was used to evaluate the adherence of health workers to the recommended intrapartum guidelines for the prevention of MTCT of HIV in Kenya, 2012 (3). These included:

- HIV testing before or during labour and delivery
- Minimizing vaginal examinations
- Using aseptic techniques during delivery
- Avoiding routine artificial rupture of membranes
- Avoiding unnecessary trauma during labour and delivery
- Reducing the risk of PPH
- Use of safe blood transfusion services
- Providing the appropriate mode of delivery

During care and delivery of parturients, a research assistant checked the prophylactic therapy for HIV HCWs offered their patients. They also recorded the mode of delivery, initiation of breastfeeding, support during labour, and the management of delivery and recorded their findings on an observation sheet. Finally, qualitative data were collected from health workers through Key Informant Interviews (KIIs) to identify the factors influencing utilization of intra-partum obstetric guidelines of MTCT of HIV. Voice recorders were used during KII interviews.

Data analysis: Data from questionnaires and observation sheets were extracted and entered into a STATA 13.0 (StataCorp LP, Texas, USA) worksheet. To determine the adherence of health workers at MDH to the recommended intrapartum obstetric guidelines for PMTCT of HIV, we generated adherence scores by first assigning a score of "1" for good PMTCT practices and "0" for wrong practices. Then, the scores were summed into an overall adherence score, which was converted to a percentage and re-categorized either as non-adherence (<75%) or adherence (75+%). The demographic data of health workers were computed as proportions and visualized on tables. Tests for statistical significance were done using the Chi-square test at 95% confidence level.

Ethical consideration: Ethical approval was sought from KNH/UoN Ethics Review Board before commencement of the study. Informed consent was sought before data collection and the personal information of respondents were not captured. PMTCT education pamphlets were distributed for training.

Results

Demographic characteristics of parturients: Throughout our study, 110 health workers were interviewed and observed. A majority (50.9%) were aged between 25 to 34 years. Females (65.5%) were more than males (34.5%). Most respondents (63.6%) had attained tertiary education. University graduates constituted 29.1% of workers with a tertiary level education. In terms of qualification, most respondents (38.2%) were nurses followed by Clinical Officers (COs) (25.5%). Medical Offices (MOs) were the least at 18.2%. Most health workers (58.2%) had an experience of less than one year (Table 1).

Table 1: Demographic characteristics of health workers

		Frequency (n)	(%)
Age (years)	20-24	34	30.9
	25-34	56	50.9
	35+	20	18.2
Gender	Female	72	65.5
	Male	38	34.5
Education level	Primary	6	5.5
	Secondary	2	1.8
	Tertiary	70	63.6
	University	32	29.1
Marital status	Single	54	49.1
	Married	56	50.9
Qualification	MO	20	18.2
	CO	28	25.5
	Nurse	42	38.2
	Midwife	20	18.2
Duration since qualification (year)	<1	36	32.7
	1-2	30	27.3
	3-4	22	20.0
	4+	22	20.0
Duration in labour ward (years)	< 1	64	58.2
	1-2	28	25.5
	3-4	10	9.1
	4+	8	7.3

Knowledge of intrapartum protocols of PMTC of HIV: All the 110 health care workers interviewed were aware of PMTCT of HIV. Even though only 41.8% had undergone formal training on PMTCT of HIV, a majority (92.7%) were aware of the ARV protocols for PMTCT of HIV. Knowledge of breastfeeding protocols for PMTCT of HIV was universal (100%), while 87.3% were aware of the recommended intrapartum methods for PMTCT of HIV (Table 2). The level of knowledge on intrapartum methods of PMTCT did not vary significantly by the age of respondents. Even though the odds of awareness was lower in the 25-34-year-old group (OR=0.29 (0.06-1.4), p=0.11) and the 35+ old age group (OR=0.56 (0.07-4.3), p=0.58) compared to 20-24-year-old, relationships were not statistically significant. Gender (p=0.05) and qualification (p=0.57) did not influence the awareness of health workers on intrapartum methods of PMTCT of HIV as well. However, a relationship between PMTCT training and the awareness on intrapartum methods of PMTCT of HIV was evident. The odds of health workers being aware of intrapartum methods of PMTCT of HIV was 11 times higher among personnel with training on intrapartum PMTCT (OR=11 (2.3-52), p<0.01) (Table 2).

Table 2: Knowledge of intrapartum obstetric methods of PMTCT of HIV by health workers

		Intrapartum PMTCT awareness			
		Yes	No	OR (95% CI)	Sig.
Age (years)	20-24	32 (33.3)	2 (14.3)	reference	
	25-34	46 (47.9)	10 (71.4)	0.29 (0.06-1.4)	0.11
	35+	18 (18.8)	2 (14.3)	0.56 (0.07-4.3)	0.58
Gender	Female	66 (68.8)	6 (42.9)	2.9 (0.93-9.2)	0.05
	Male	30 (31.3)	8 (57.1)	0.34 (0.11-1.1)	0.05
Education	Primary	6 (6.3)	0 (0.0)	reference	
	Secondary	0 (0.0)	2 (14.3)	0.0 (0.00-1.0)	<0.01
	Tertiary	58 (60.4)	12 (85.7)	0.3 (0.02-6.8)	0.27
	University	32 (33.3)	0 (0.0)	5.3 (0.29-98)	0.21
Qualification	MO	20 (20.8)	0 (0.0)	reference	
	CO	24 (25.0)	4 (28.6)	0.6 (0.09-3.6)	0.57
	Nurse	36 (37.5)	6 (42.9)	0.6 (0.11-3.3)	0.55
	Midwife	16 (16.7)	4 (28.6)	0.4 (0.07-2.5)	0.31
PMTCT training	Yes	62 (64.6)	2 (14.3)	11 (2.3-52)	<0.01
	No	34 (35.4)	12 (85.2)	0.1 (0.0-0.43)	<0.01

Adherence to intrapartum protocols of PMTCT of HIV: A majority of health workers (66.82%) did not adhere to recommended intrapartum obstetric guidelines for PMTCT. Only 38.15% practiced nine or more of the 12 recommended PMTCT protocols (75% cut off) during delivery. Adherence to standard intrapartum protocols such as the minimization of vaginal examinations (87.3%) and discouraging prolonged labour (87.3%) was almost universal. A majority of HCWs practiced aseptic delivery (70.9%) and avoided artificial rupturing of membranes (70.9%). However, only 34.5%, 29.1%, and 27.3% cleansed babies, cleansed the vagina of parturients with antiseptics after rupture of membranes, and presented parturients the option of elective Caesarean section (CS) before the onset of labour.

Several factors influenced the adherence to intrapartum guidelines for PMTCT. More women than men adhered to the intrapartum PMTCT of HIV (OR=3.4 (1.4 to 8.3), p<0.01). The odds of adherence dropped significantly among health care workers with a tertiary (OR=0.1 (0.0 to 0.76), p<0.01) and university (OR=0.1 (0.0-1.1), p=0.02) level of

education. Respondents who had spent 1-2 years in a maternity ward were 2.9 times more likely to adhere to recommended intrapartum protocols for PMTCT of HIV than those who had spent less than a year in wards (OR=2.9 (1.2 to 7.3), p=0.02). PMTCT training also influenced adherence, with the odds being higher among the health workers with formal training (OR=2.8 (1.3-6.2), p=0.01) (Table 3).

Table 3: Adherence to intrapartum obstetric methods of PMTCT of HIV by health workers

		Adherence to protocols			
		Yes	No	OR (95% CI)	Sig.
Age (years)	20-24	10 (23.8)	24 (35.8)		reference
	25-34	26 (61.9)	30 (44.1)	2.1 (0.84-5.1)	0.11
	35+	6 (14.3)	14 (20.6)	1.0 (0.31-3.4)	0.96
Gender	Female	34 (81.0)	38 (55.9)	3.4 (1.4-8.3)	<0.01
	Male	8 (19.0)	30 (44.1)	0.3 (0.12-0.74)	<0.01
Education	Primary	6 (14.3)	0 (0.0)		reference
	Secondary	2 (4.8)	0 (0.0)	0.3 (0.01-8.2)	0.49
	Tertiary	24 (57.1)	46 (67.6)	0.1 (0.0-0.76)	<0.01
	University	10 (23.8)	22 (32.4)	0.1 (0.01-1.1)	0.02
Qualification	MO	6 (14.3)	14 (20.6)		reference
	CO	16 (38.1)	12 (17.6)	3.1 (0.92-10)	0.06
	Nurse	12 (28.6)	30 (44.1)	0.9 (0.29-3.0)	0.91
	Midwife	8 (19.0)	12 (17.6)	2.6 (0.82-8.3)	0.10
Experience (years)	< 1	20 (47.6)	44 (64.7)		reference
	1-2	16 (38.1)	12 (17.6)	2.9 (1.2-7.3)	0.02
	3-4	4 (9.5)	6 (8.8)	1.5 (0.37-5.8)	0.58
	4+	2 (4.8)	6 (8.8)	0.7 (0.14-4.0)	0.72
PMTCT training	Yes	24 (57.1)	22 (32.4)	2.8 (1.3-6.2)	0.01
	No	18 (42.9)	46 (67.6)	0.3 (0.16-0.79)	0.01

Discussion

The Kenya National AIDS Strategic plan 2000-2010 recommends that HCW should adhere to a set of clinical standards that lower the risk of vertical transmission of HIV (6). This study was designed to evaluate the adoption of these intrapartum strategies for PMTCT of HIV in a peri-urban hospital in Kenya. HCWs were responsible for the implementation of protocols of PMTCT of HIV. Unfortunately, the intrapartum PMTCT program in our study site did not meet the recommendations of the national guidelines in Kenya for PMTCT of HIV. HIV positive parturients in active labour received sub-optimal care. Similar results have been found at the Kenyatta National Hospital (KNH) and Pumwani Hospital in Kenya (7). HCWs often ignored recommended protocols such as cleansing of neonates after birth and use of antiseptics after artificial rupture of membranes. Moreover, high-risk parturients were not offered the option of elective Caesarean section (CS) during delivery. Studies have linked an adherence to such intrapartum protocols with a low risk of vertical transmission of HIV to babies (8–10).

A few individual and hospital factors were identified as barriers for adherence to intrapartum protocols for PMTCT of HIV. Compared to the knowledge of PMTCT of HIV protocols on ARV use or breastfeeding, knowledge on intrapartum protocols of PMTCT of HIV was slightly lower. In Nigeria, similar

results have been reported because of poor training of HCWs (10). We got comparable results. In the study site, about 58% of HCWs had sufficient training on intrapartum protocols of PMTCT of HIV, even though it is a requirement in Kenya. Moreover, inexperienced nursing students and HCWs who had spent less than one year in the labour ward were more likely to fail to adhere to the recommended intrapartum protocols of PMTC of HIV than consultants and doctors. Their knowledge was mainly from a dated PMTCT of HIV chart pinned in delivery rooms, which had little emphasis on intrapartum guidelines of PMTCT of HIV. To improve compliance, there is a need for continuous training of HCWs in labour wards on intrapartum PMTCT of HIV. Regular training has been linked to the reduction in MTCT of HIV rates reported in neighbouring African countries such as Tanzania (11). The supervision of trainee nurses stationed in labour wards by experienced HCWs can also improve adherence.

Reports of facility-associated barriers leading to low adherence to intrapartum protocols for PMTCT of HIV were recurrent during FDGs and KIIs. Most health workers mentioned staff shortages and heavy workload as the main reasons for non-adherence. This corresponds with the results of Watt *et al*. (12) in South Africa. Because of low pay, many HCWs in peri-urban public hospitals seek employment in the private sector, which offers better pay and adequate resources to enable them perform their duties professionally (13). As such, it leads to a shortage of staff which is compounded by a heavy workload that came about because of a rise in patient numbers in public hospitals after a declaration by the government that maternity services in all public hospitals in Kenya are free (14,15). While struggling to deliver parturients with HIV, HCWs forget to follow intrapartum protocols of PMTCT of HIV with adverse outcomes. Midwives also resort to using nursing students to offset workload, most of whom are unaware of intrapartum protocols for PMTCT of HIV. Elimination of such barriers can boost adherence.

Conclusions

The knowledge of intrapartum obstetric methods of PMTCT of HIV is high among HCWs. However, adherence to the said protocols is poor because of insufficient training of HCWs. The stationing of trainee nurses in delivery units without adequate supervision is a risk factor for non-adherence to intrapartum protocols for PMTCT of HIV. Administrators of hospitals should address institutional barriers for PMTCT adoption such as staff shortage and workload to be able to improve the quality of service to HIV positive parturients delivering naturally.

Limitations

We did not evaluate whether parturients deemed the level of service they received during active labour, delivery, and post-partum, which could help us make inferences. We relied solely on the observations of research assistants, but who were trained on the modalities of this study.

Conflict of interest

The authors have declared no conflict of interest.

Acknowledgments

To the health workers at Mbagathi District Hospital.

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Original paper

Prevalence of Cirrhotic Cardiomyopathy among Patients with Liver Cirrhosis at Kenyatta National Hospital

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Abstract

Background: Cardiac dysfunction is not uncommon in liver cirrhosis. Cirrhotic cardiomyopathy is an impaired contractile responsiveness to stress and/or abnormal diastolic function with associated electrophysiological abnormalities in lack of other known cardiac diseases. This form of cardiac disorder bears significant morbidity and mortality particularly after invasive procedures.

Objective: To determine the prevalence of cirrhotic cardiomyopathy among patients with liver cirrhosis at Kenyatta National Hospital.

Design: This was hospital based descriptive cross-sectional study.

Setting: Kenyatta National Hospital out-patient liver clinic and medical wards, Nairobi, Kenya.

Subjects: Forty-four patients with liver cirrhosis presenting to Kenyatta National Hospital.

Interventions: All patients underwent resting echocardiography and 12-lead electrocardiogram.

Results: Forty-four patients were recruited. The mean age of the participants was 44 years. Twenty seven (61.4%) were male. Hepatitis B infection (38.6%) and chronic alcohol consumption (38.6%) were the two leading aetiology of liver cirrhosis. Out of 44 patients, 17 (38.6%) belonged to class A, 16 (36.4%) to class B, and 11 (25.0%) to class C. Three (6.8%) patients were found to have systolic dysfunctions. Nineteen (43.2%) diastolic dysfunction; more than three quarter (94.7%) of these had grade 1 diastolic dysfunction. Prolonged (>440ms) QTc interval was present in 25 (56.8%) patients. Cirrhotic cardiomyopathy was recorded in 43.2% of the study population. Liver disease severity did not show correlation with the cardiomyopathy.

Conclusion: The prevalence of cirrhotic cardiomyopathy as mainly driven by diastolic and systolic dysfunction was high in this black African population of liver cirrhosis. QTc interval prolongation was common in our study. The severity of liver disease did not show association with the presence of cirrhotic cardiomyopathy.

Key words: Liver cirrhosis, Cirrhotic cardiomyopathy, Echo, ECG, Systolic dysfunction, Diastolic dysfunction, QTc interval

Introduction

Cirrhosis causes significant morbidity and mortality worldwide; it is associated with wide-ranging cardiovascular abnormalities which are now described as cirrhotic cardiomyopathy. According to the World Congress of Gastroenterology of 2005, cirrhotic cardiomyopathy is a chronic cardiac dysfunction with impaired contractile responsiveness to stress stimuli and/or impaired diastolic relaxation with electrophysiological abnormalities in the absence of other known cardiac diseases (1). Cirrhotic cardiomyopathy occurs in variable degrees in patients with liver cirrhosis with an estimated prevalence of 40% to 50% (2).

Cirrhotic cardiomyopathy is often under-diagnosed as it is not widely recognized because most of the patients are asymptomatic at rest with overt heart failure being uncommon. This latent cardiomyopathy is recognized when patients with liver cirrhosis experience pathological, physiological, or pharmacological stress. Cirrhotic cardiomyopathy assumes clinical importance in the setting of events that challenge the heart such as liver transplant surgery and the insertion of Transjugular

Intrahepatic Porto-systemic Shunts (TIPS). These stressful procedures can precipitate acute cardiac failure due to haemodynamic instability (2).

Materials and methods

Area of study: The study was carried out at KNH outpatient liver clinic and inpatient medical wards from March to June 2018. KNH is a public tertiary teaching and referral hospital. The hospital runs weekly based liver clinic.

Study subjects: The study participants consisted of patients with diagnosis of liver cirrhosis that were on follow-up at KNH liver clinic or admitted to the medical wards.

Study design: Descriptive cross-sectional study.

Inclusion criteria: These included patients who were ≥13 years diagnosed with liver cirrhosis irrespective of aetiology.

Ethical considerations: Approval to perform the study was sought from Kenyatta National Hospital-University of Nairobi Ethical and Research committee (KNH-UoN ERC).

Data collection: The study subjects were recruited from Kenyatta National Hospital liver clinic and inpatient medical wards by the principal investigator (PI). Patients meeting the inclusion criteria were given information about the study and asked to participate in the study. Eligible patients agreeable to take part in the study signed a certificate of consent. All study subjects underwent echocardiography by trained echocardiography technician and recorded videos were reviewed by two cardiologists.

Philips iE33 machine equipped with S5-1 Sector Array Transducer was used. Modified Simpson's technique in apical 4 chamber view was used to calculate Left Ventricular (LV) Ejection Fraction (EF). Pulsed Wave Doppler echocardiography in the setting of apical four chamber view and the sample volume placed at the tips of the mitral leaflets was used to obtain trans-mitral LV filling velocity measurements from three successive cardiac cycles to measure the peak early diastolic flow velocity (E), the peak of atrial flow velocity (A) and E/A ration.

Data analysis: The data collected was analyzed by means of SPSS and presented in tables and graphs. The accepted level of significance was 5%.

Results

The mean age of the study participants was 44 years, 27 (61.4%) were males. Liver disease severity was characterized according to child pugh score. Out of 44 patients, 17 (38.6%) belonged to class A, 16 (36.4%) belonged to class B, and 11 (25.0%) belonged to class C (Table 1).

Table 1: Socio-demographic and clinical characteristics (n=44)

Characteristic	No. (%)
Age, (Mean in years, ± SD)	44.0 (12.2)
Gender (n, %)	
Male	27 (61.4)
Female	17 (38.6)
Marital status (n, %)	
Single	14 (31.8)
Married	27 (61.4)
Widowed	3 (6.8)
Education level (n, %)	
None	2 (4.5)
Primary	22 (50.0)
Secondary	18 (40.9)
Tertiary	2 (4.5)
Occupation (n, %)	
Self employed	21 (47.7)
Employed	4 (9.1)
Unemployed	17 (38.6)
Retired	2 (4.5)
Child Pugh score (n, %)	
A	17 (38.6)
B	16 (36.4)
C	11 (25.0)
Jaundice (n, %)	
Yes	26 (59.1)
No	18 (40.9)
Ascites (n, %)	
Yes	26 (59.1)
No	18 (40.9)

Regarding the aetiology of liver cirrhosis, 17 (38.6%) patients had hepatitis B infection and another 17 had history of chronic alcohol consumption. Two patients had both viral hepatitis and history of chronic alcohol intake. Two (4.5%) patients had auto- immune liver disease and 6 (13.6%) patients had unknown aetiology of liver cirrhosis (Figure 2).

Figure 1: Liver cirrhosis aetiology of the participants

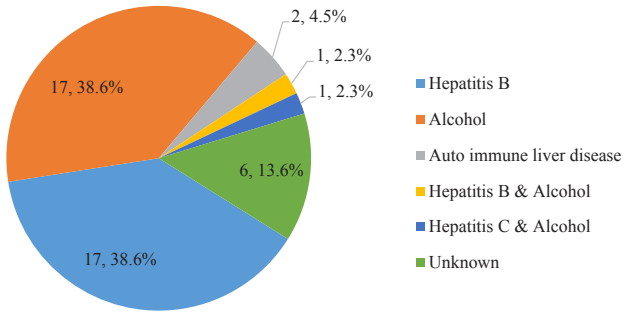


Table 2: Systolic and diastolic dysfunction, and QTc interval of the study participants

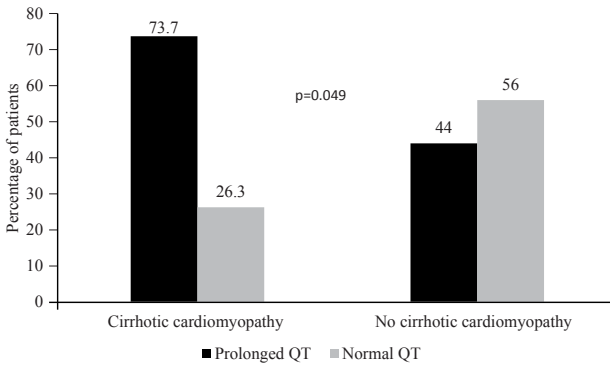
Echocardiographic and ECG findings	All study participants	
	No.	(%)
Systolic function (LVEF):		
Abnormal (<55 %)	3	6.8
Normal (>55 %)	41	93.2
Diastolic dysfunction	19	43.2
E/A ratio		
<1	18	40.9
>1.5	1	2.3
>1	26	59.1
Deceleration time (DT)		
>200 ms	18	40.9
<200 ms	26	59.1
IVRT (ms)		
>80	18	40.9
<80	26	59.1
Diastolic dysfunction grades		
Grade I	18	94.7
Grade II	0	
Grade III	1	5.3
QTc interval		
Prolonged (>440 ms)	25	56.8
Normal (<440 ms)	19	43.2

IVRT= Isovolumetric Relaxation Time; QTc= Corrected QT interval

Only 3 (6.8%) patients were found to have systolic dysfunction. Eighteen (40.9%) participants had age-adjusted E/A ratio <1. One (2.3%) patient had E/A ration >1.5, deceleration time (DT) <160ms, and isovolumetric relaxation time (IVRT) <70ms. Overall, 19 (43.2%) patients were found to have diastolic dysfunction based on the above parameters. Eighteen (94.7%) had grade 1 diastolic dysfunction, only 1 (5.3%) patient had grade 3 diastolic dysfunction. Resting 12-lead ECG showed normal QTc interval in 19 (43.2%) patients while 25 (56.8%) patients had prolonged (>440ms) QTc interval (Table 2).

Out of 44 study participants, 19 (43.2%) patients had evidence of cirrhotic cardiomyopathy indicated by systolic and/or diastolic dysfunction. Three (6.8%) patients had both systolic and diastolic dysfunctions while 16 (36.4%) had only diastolic dysfunction. Nine (47.4%) of the patients who had cirrhotic cardiomyopathy were alcoholic while another 9 (47.4%) were non-alcoholic. One (5.3%) patients had both hepatitis C infection and history of chronic alcohol intake. Out of 19 patients with cirrhotic cardiomyopathy, 14 (73.7%) of them had prolonged (>440 ms) QTc interval. Chi square statistical test applied to this have showed significant (P=0.049) association between QTc prolongation and cirrhotic cardiomyopathy (Figure 2).

Figure 2: Distribution of QTc interval prolongation among study participants



Out of 19 patients with cirrhotic cardiomyopathy, 5 (26.4%) were child pugh class A, 7 (36.8%) were class B, and 7 (36.8%) class C. The severity of liver disease as assessed by child Pugh score did not show significant association with cirrhotic cardiomyopathy (p=0.117). During study procedures, other echocardiographic and ECG abnormalities were observed (Table 3).

Table 3: Other echocardiographic and ECG findings

Echo and ECG findings	All study participants	
	No.	(%)
Pulmonary hypertension	11	25
Mild	10	90.9
Moderate	1	9.1
Tricuspid regurgitation	16	36.4
Mild	14	87.5
Moderate	2	12.5
Mitral regurgitation	6	13.6
Mild	3	50.0
Moderate	2	33.3
Severe	1	16.7
Aortic regurgitation	1	2.3
LVH	5	11.4
Pleural effusion	6	13.6
Pericardial effusion	3	6.8
Premature Ventricular Contractions (PVCs)	4	9.1
Sinus tachycardia	4	9.1
Sinus bradycardia	2	4.5
1st degree AV block	2	4.5
Low voltage	3	6.8
RBBB	1	2.3
Left axis deviation	1	2.3
Right axis deviation	1	2.3
Atrial premature complex	1	2.3

Echo= Echocardiography; ECG= Electrocardiogram; RBBB= Right Bundle Branch Block; LVH= Left Ventricular Hypertrophy

Discussion

The study was designed to find out the prevalence of cirrhotic cardiomyopathy among liver cirrhosis patients at Kenyatta National Hospital. Regarding the stage of liver disease, majority (75%) of the patients were in child Pugh class A & B. Alcohol and hepatitis B infection were the main causes of liver cirrhosis in this study. In this study, 6.8% of the participants had systolic dysfunction on resting echocardiography. In Portugal, Barbosa *et al* (3) reported systolic dysfunction in 38.5% of cirrhotic patients in whom, alcohol was the major aetiology of cirrhosis. As in our study, most of the patients were in child Pugh class A & B. Barbosa *et al* (3) used stress echocardiography with intravenous infusion of dobutamine instead of resting echocardiography to evaluate left ventricular systolic function. Another study by Kim *et al* (4) in Korea showed left ventricular blunted response defined by <10% increase of ejection fraction after dobutamine infusion in 25.4% of liver cirrhosis who had normal systolic function at rest. Systolic dysfunction is commonly manifested during physiologic, pharmacologic or pathologic stressful conditions in cirrhosis patients. The higher numbers of systolic dysfunction in these two studies compared to our study could be due to the different echocardiographic modality used in these studies. This supports the concept of subtle systolic dysfunction in liver cirrhosis. Stress echocardiography is an ideal tool to unmask this latent contractile dysfunction.

In this study, diastolic dysfunction was present in 43.2% of the cases, mainly driven by reduced E/A ratio. This is consistent with what is reported in other several studies. In India, Patil *et al* (5) reported diastolic dysfunction in 48.3% of the study cases. Patil *et al* (5) used Model for End stage Liver Disease (MELD) score to assess liver disease severity and most of the patients were in MELD stage 1. This is comparable to child Pugh class B in present study; so, liver disease severity was almost the same with our patients. In Egypt, Eldeeb *et al* (6) found 66.6% of diastolic dysfunction in non- alcoholic liver cirrhosis patients. Majority of the cases were in child Pugh class B & C compared to our study where most of the cases were in classes A & B. Another study in Egypt by Mashahit *et al* (7) reported diastolic dysfunction in 60% of liver cirrhosis patients. Studies have shown that diastolic dysfunction is well correlated with liver disease severity (8). We evaluated the association between diastolic dysfunction severity and severity of cirrhosis in non-alcoholic cirrhotic patients. This cross-sectional study was conducted on all nonalcoholic cirrhotic patients who were admitted in Rasht Razi hospital the Cancer of Guilan Province, north of Iran, from January 2011 to March 2012. Severity of cirrhosis was evaluated by Child-Pugh score. A 12-lead surface ECG and echocardiographic studies were performed. We used a HDI 3000 (Philips ATL, Bothell, WA, USA). Some of the differences observed in prevalence of diastolic dysfunction across different populations are attributable to liver disease severity difference in different study populations.

Most of the studies on cirrhotic cardiomyopathy used mitral E/A ratio for diastolic dysfunction assessment. In our study we similarly applied age-adjusted E/A ratio to detect diastolic dysfunction.

In this study we recorded 43.2% prevalence of cirrhotic cardiomyopathy determined by presence

of left ventricular systolic or diastolic dysfunction irrespective of QTc interval prolongation. The high burden of cirrhotic cardiomyopathy in this study is mostly driven by diastolic dysfunction. Our findings are consistent with what other studies reported in populations of Europe, America, Asia and Africa. Barbosa *et al* (3) in Portugal reported prevalence of 61.5% of cirrhotic cardiomyopathy. Barbosa *et al* (3) used dobutamine stress echocardiography to detect systolic dysfunction which commonly not revealed by resting echocardiography that we used in our study. This may explain the higher prevalence of cardiomyopathy in this study compared to our findings.

In USA, Belay *et al* (9) found 51.1% prevalence of cirrhotic cardiomyopathy. Belay *et al* (9) used both systolic and diastolic dysfunction, and prolonged QTc interval to define cirrhotic cardiomyopathy. Use of prolonged QTc interval as defining criteria for cirrhotic cardiomyopathy and the larger sample size may explain the slightly higher figures of cirrhotic cardiomyopathy in this study compared to our findings. Studies on similar populations in India and Pakistan had reported results closer to our findings. Sakthi *et al* (10) in India studied the prevalence of cirrhotic cardiomyopathy by using resting echocardiographic findings of systolic and diastolic dysfunction. He found 44.6% prevalence of cirrhotic cardiomyopathy. In Pakistan, Nisar *et al* (11) reported 49.0% prevalence of cirrhotic cardiomyopathy. In Egypt, a study conducted by Abdel-bary *et al* (12) showed 64% prevalence of cirrhotic cardiomyopathy in 66 HCV-related liver cirrhosis patients. This Egyptian study had higher sample size and higher child Pugh class C indicating that majority of the participants got advanced liver cirrhosis compared with ours.

The present study showed high prevalence of cirrhotic cardiomyopathy in this African black population. Published studies have revealed that cirrhotic cardiomyopathy is linked to poor survival and significant mortality due to heart failure and arrhythmias flowing invasive interventions such as hepatic transplantation and TIPS (13-15). Cirrhotic cardiomyopathy has also been related with the development of hepato-renal syndrome as it may cause alterations in the effective circulatory blood volume. Sepsis, such as spontaneous bacterial peritonitis generates metabolic stress due to increased production of inflammatory cytokines (16). This may result in an overt heart failure in cirrhotic patients. Therefore; perioperative and post-operative cardiac evaluation by echocardiography and ECG, and careful monitoring of cardiac decompensation in all stressful conditions is a reasonable recommendation. Hepatic transplantation is the sole definitive therapy for advanced liver cirrhosis and it is reported to resolve liver cirrhosis related cardiovascular disorders (17).

In our study, we recorded 56.8% prevalence of QTc interval prolongation that was highly present in subjects with evidence of cirrhotic cardiomyopathy. Prolongation of QTc interval is not uncommon in liver cirrhosis as several previous studies revealed. In Portugal, Borbosa *et al* (3) documented QTc prolongation in 68.8% of liver cirrhosis patients. Parkash *et al* (18) in Pakistan reported 35% prevalence of QTc prolongation among liver cirrhosis patients, 33.8% of the cases in their study were on beta-blocker therapy which shortens QTc interval; this may explain the difference in findings with the present study. Pourafkari *et al* (19) in Iran reported QTc prolongation in 63.5% of cirrhotic cases. The bigger sample size of this study may explain the difference with our study. Long QTc interval is shown to be associated with lower survival rate and risk of arrhythmias in patients with liver cirrhosis (20,21). Therefore, it is worth to monitor QTc interval in subjects with advanced liver cirrhosis with attention to any modifiable cause of QTc prolongation such as medications and electrolyte imbalance.

This study did not show correlation between cirrhotic cardiomyopathy and child Pugh score ($p = 0.117$). Previous studies reported positive correlation while others found negative correlation between cirrhotic cardiomyopathy and child Pugh score. A study by Perumal *et al* in India showed association of cirrhotic cardiomyopathy and the stage liver dysfunction as determined by child Pugh score. In this study, majority (66%) of the subjects were in child Pugh class C. Another Indian study by Thirumal *et al* also established association between child Pugh score and the occurrence of cirrhotic cardiomyopathy. This study also had higher proportion (70.7%) of child Pugh class C cases compared to the present study. Lack of association between cirrhotic cardiomyopathy and child Pugh severity score in our study may be due to inadequate sample size. Our study had limitation that resting echocardiography was used to evaluate systolic function. This may have underestimated the burden of systolic dysfunction.

Our study concluded that the prevalence of cirrhotic cardiomyopathy as mainly driven by diastolic dysfunction was high in this black African population of liver cirrhosis. Long QTc interval was common in this study. This was significantly higher in patients with

cirrhotic cardiomyopathy. Therefore; we recommend cardiac evaluation by 2-D echocardiography and 12-lead ECG for patients with liver cirrhosis.

Acknowledgements

I am very grateful to my supervisors for their contribution in ideas, feedback and advice in this research project. I also thank the hospital administrators in Kenyatta National Hospital for their permission and co-operation, during the period of this work.

Conflict of interest

There is no conflict of interest in this study.

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Review article

HIV-Associated Malignancies: What we Know, the Challenges and Opportunities for Intervention

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Abstract

Background: HIV-infected individuals have an increased propensity to develop malignancies. The occurrence of a high number of cases of Kaposi's Sarcoma (KS) was noted early in the AIDS epidemic. Thus, cancer and HIV infection have been inextricably linked since the beginning of the AIDS pandemic. Kaposi's sarcoma (KS), Non-Hodgkins Lymphoma (NHL), and Invasive Cervical Cancer (ICC) have been found to have high incidence in HIV-infected persons and are classically referred to as AIDS-Defining Malignancies (ADM). However, as antiretroviral therapy becomes more widespread, the spectrum of neoplasms in the HIV infected has changed with a decline in KS and NHL but a relative increase in other tumour types referred to as Non-AIDS-Defining Malignancies (NADMs). NADMs are now noted to be a major cause of morbidity and mortality among HIV-infected persons. The causes of increased malignancies are poorly understood but are thought to be multifactorial and include a possible direct pro-oncogenic effect of HIV, chronic inflammation, persistent immune and antiretroviral toxicity. It is not clear yet how antiretroviral therapy affects the risk of NADM. Here we review the literature and evidence around HIV and associated malignancies and discuss the challenges and opportunities for possible interventions.

Objective: The purpose of this review is to describe the epidemiology of cancers that occur at an elevated rate among people with HIV infection in the current treatment era, including discussion of the aetiology.

Conclusions: The epidemiology of cancer among HIV-infected people has evolved since the beginning of the HIV epidemic with particularly marked changes since the introduction of modern treatment. Public health interventions aimed at prevention and early detection of cancer among HIV-infected people is needed.

Key words: HIV, Cancer, Epidemiology, Rates, Immunosuppression

Introduction

The Acquired Immune Deficiency Syndrome (AIDS) pandemic was first reported in 1981 with patients typically presenting with opportunistic infections such as pneumonia mainly caused by *Pneumocystis jirovecii* (formerly known as *P. carinii*), and cytomegalovirus infections. It was quickly learned that patients infected with Human Immunodeficiency Virus (HIV) also have a high risk of developing several forms of cancer (1). These malignancies may arise when the immune system is damaged and the CD4 T-cell count is low. Virally induced neoplasia, such as Kaposi's sarcoma (associated with human herpes virus 8, HHV8), cervical cancer (associated with human papilloma virus, HPV) and aggressive non-Hodgkin's lymphoma (associated with Epstein-Barr virus, EBV) have been defined as AIDS-related malignancies. However, with the advent of combination antiretroviral therapy (cART) in 1996, both the risk of opportunistic infections and the incidence of AIDS-related malignancies have declined. Especially, the occurrence of Kaposi's sarcoma has decreased remarkably.

Cancer and the HIV Epidemic

Cancer has been a major feature of the HIV epidemic from the beginning, when cases of Kaposi's sarcoma and Non-Hodgkin's Lymphoma (NHL) were among the first reported manifestations of what later came to be known as AIDS (2-5). Moreover, despite marked improvements in HIV treatment and outcomes, cancer continues to comprise a sizeable part of the disease burden and mortality attributable to HIV infection (6,7). Research on the epidemiology of cancer among HIV-infected people provides important information to help public health professionals, clinicians and patients optimize overall health outcomes in the HIV population.

AIDS-defining malignancies

Cancer remains a major cause of morbidity and mortality in HIV-infected individuals, accounting for approximately one-third of all deaths in these patients (5,8). In fact, HIV patients have a higher risk of mortality from a tumour than from an AIDS-defined infection, with aggressive non-Hodgkin's lymphoma being the most frequent event. Therapy of these malignancies remains a challenge for the attending

oncologist who, besides needing detailed knowledge about the tumour itself and the therapeutic options, must deploy experience in the use of antiviral medication as an essential part of treatment.

HIV-infected individuals have a substantially elevated risk of developing Kaposi's sarcoma, certain high-grade NHLs and cervical cancer—all of which are considered AIDS-defining malignancies; that is, they mark the onset of clinically relevant immune suppression. HIV-infected people have risk that is 330-fold elevated for Kaposi's sarcoma, 10-fold elevated for NHL and three-fold elevated for cervical cancer compared with the general population (9). As a result of the extraordinary elevation in Kaposi's sarcoma risk, the majority of Kaposi's sarcoma cases during the pre-HAART era were among HIV-infected people (10). NHL is a heterogeneous entity, and risk among HIV-infected people is most strongly elevated for the three AIDS-defining sub-types, namely: diffuse large B-cell lymphoma, Burkitt's lymphoma and primary central nervous system lymphoma (11).

The three AIDS-defining malignancies are caused by viruses: Kaposi's sarcoma-associated Herpes Virus (KSHV) for Kaposi's sarcoma; Epstein-Barr virus (EBV) for most cases of the lymphomas closely linked to HIV, and; Human Papilloma Virus (HPV) for cervical cancer. One contribution to the high risk among HIV-infected people is the high prevalence of viral co-infection with KSHV (which is transmitted sexually among both men and women). For Kaposi's sarcoma and NHL, the high risk is also strongly related to advancing immunosuppression, as manifested by declines in circulating CD4 cell counts (12). The elevated risk of cervical cancer in HIV-infected women is partly due to increased sexual acquisition of HPV and incomplete use of preventive screening. The risk of cervical cancer increases with declining CD4 cell count (13,14). Thus, epidemiologic evidence points to an aetiologic model whereby the AIDS-defining cancers arise through loss of immunologic control of oncogenic viral infections.

Non-AIDS-defining malignancies

HIV-infected people also have an elevated risk for some of the remaining (non-AIDS-defining) malignancies, some of which—such as anal cancer, which is caused by HPV—are also caused by viral infections. Risk for this cancer is strongly elevated among HIV-infected people, particularly among Men having Sex with Men (MSM), who are likely to acquire anal HPV infection through sexual intercourse.

MSM with AIDS manifest an approximately 90-fold increase in anal cancer compared to the general population (15). Their risk is also elevated for Hodgkin's lymphoma, especially for cases linked to EBV. Advancing immunosuppression contributes to risk for both anal cancer and Hodgkin's lymphoma, although the relationships appear to be more complex than for KS and NHL (16,17). Hepatocellular carcinoma risk is also elevated among HIV-infected individuals, related to a high prevalence of co-infection with hepatitis B and C viruses (HBV and HCV), which are transmitted sexually and via blood- (e.g. injection drug use). However, immunosuppression in HCV-related cases is less clear.

HIV-infected people also have an increased risk of lung cancer. In developed countries during the pre-HAART era, lung cancer risk was 3-5 fold elevated in HIV-infected individuals compared with the general population (15,18). Increase partly reflects a high prevalence of tobacco use (19) and lung cancer cases that do arise are almost entirely among current or former smokers.

Pathogenesis of malignancy in HIV

HIV-related malignancy is related to a combination of factors including decreased immune tumour surveillance from immunosuppression, chronic antigenic stimulation, immune dysregulation, and co-infection with oncoviruses. The exact role that HIV infection plays in tumourigenesis is not very clear, but HIV is known to cause severe immune system deficiency as well as dysregulation of the immune system. This may lead to impaired immune surveillance, increased immune activation and decreased clearance of transformed cells.

In addition, there is also evidence that HIV directly activates or promotes tumour oncogenes or proto-oncogenes as well as suppresses tumour suppressor genes (20). HIV has also been found to promote genetic instability and to enhance the susceptibility of epithelial cells to the effects of certain carcinogens (21). HIV infection is associated with immune-senescence and this leads to a more rapid immune system aging, predisposing sufferers to developing cancer (22, 23).

Discussion

Cancer has been a major feature of the HIV epidemic from the beginning when cases of KS and non-NHL were among the first reported manifestations of AIDS. Moreover, despite marked improvements in HIV treatment and outcomes, cancer continues to comprise a sizeable part of the disease burden and mortality attributable to HIV infection (24).

The epidemiology of cancer among HIV-infected people has evolved since the beginning of the HIV epidemic, tracking strong patterns in cancer incidence rates and dynamic population demographics preceding and following the introduction of HAART. However, much more epidemiologic research is needed. Little information is known yet about cancer risk among people living with HIV (PLWH) for decades. Studies must continue to monitor cancer rates over time in the HIV-infected population and estimates of future rates and burden are needed to identify targets for cancer prevention and early detection, as well as to guide resource allocation. Furthermore, information is needed on the risk of cancer among HIV-infected people living in the developing world, particularly in Africa, where the HIV epidemic is most concentrated. Large population-based studies in many of these countries are difficult because of the lack of national and regional registration of HIV and cancer cases and a dearth of resources and expertise in disease surveillance, which is sorely needed.

In the end, targeted public health interventions aimed at the prevention and early detection of cancer are needed to reduce cancer risk among HIV-infected people. Additional public heath interventions such as smoking cessation programmes and treatment of HBV and HCV could also reduce the cancer burden in this population.

Cancer burden in HIV-infected people

With the longevity afforded by modern treatment, a 20-year old person infected with HIV today now has a projected life expectancy that is similar to that observed in the general population (25). Decline in mortality among HIV-infected individuals has resulted in the growth and aging of the HIV-infected population, which has implications for current and future cancer risk and the total burden of cases. Since cancer risk increases with age, and the HIV population is growing, the burden of HIV-infected people with cancer has also grown markedly.

While Kaposi's sarcoma and NHL has declined over time (driven by the sharply decreasing incidence rates), the total number of cases for each non-AIDS-defining cancer increased over time, largely driven by the growth and aging of the HIV-infected population, as well as increasing cancer rates for some sites (26). This pattern was seen for both non-AIDS-defining malignancies that are elevated among people with HIV (e.g. anal and lung cancers) and cancers that are common in the general population but do not occur more frequently in people with HIV (e.g. breast and prostate cancers). The total number of non-AIDS-defining cancers has exceeded the number of AIDS-defining cancers since 2003 (22,23) among people with AIDS, highlighting the changing spectrum of cancers diagnosed in this population. As the HIV-infected population continues to grow and age, the burden of cancer (particularly non-AIDS-defining cancers) will continue to rise—as will the need for cancer prevention, early detection and treatment.

HIV and cancer in the developing world

In sub-Saharan Africa, where there is a large proportion of PLWH, Kaposi's sarcoma and cervical cancer are among the most common malignancies. As in developed countries, risk for all three AIDS-defining cancers is elevated among HIV-infected people in Africa (27,28) and the onset of the HIV epidemic led to a dramatic increase in Kaposi's sarcoma incidence (29). The greatly expanding access to HAART in recent years will hopefully lead to a reduction in the incidence of AIDS-defining cancers over time. Most African countries lack population-based cancer registry data that allow an assessment of the cancer burden. Nonetheless, analyses of incidence data from cancer registries in Uganda and Botswana provide evidence for recent declines in Kaposi's sarcoma that are temporally associated with uptake of HAART (30,31).

However, the elevation in lung cancer appears higher than can be explained by smoking alone. Repeated lung infections, chronic pulmonary inflammation and/or immunosuppression may act synergistically with tobacco to promote the development of lung cancer. In contrast, HIV-infected people do not have an elevated risk for other common malignancies such as colorectal, prostate and breast cancers. Indeed, for unclear reasons, the rates of prostate and breast cancers are significantly reduced among HIV-infected people compared with the general population.

Conclusions

Although the development of cART has done much to improve overall survival and reduce the incidence of AIDS-defining cancers, other cancers have come to the forefront and have become common causes of complications and death among persons with HIV infection. As the HIV-infected population ages, a wide variety of HIV-associated cancers have become increasingly important. These cancers pose both challenges and opportunities. However, many questions remain, and addressing these will open new approaches for the prevention, diagnosis, and treatment of malignancies among the more than 35 million people worldwide who are infected with HIV.

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Case report

Closure of a Patent Foramen Ovale after Presumed Coronary Paradoxical Embolism in a Young Woman: A Case Report

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Summary

One of the most common congenital heart disease is atrial septal defect. This conditions may be asymptomatic or responsible of morbidity, mortality and reducing of life expectancy. After a paradoxical embolism, it is possible to introduce more aggressive therapeutic to avoid recurrence and the devastating effect of coronary heart disease and secondary effects of treatment on an active young patient. We report the case of a young woman without significant cardiovascular factors which presented as myocardial infarction via a patent foramen ovale associated to atrial septal aneurysm. She benefited from an amplatzer device implantation.

Key words: Myocardial infarction, Paradoxical embolism, Patent foramen ovale, Percutaneous closure

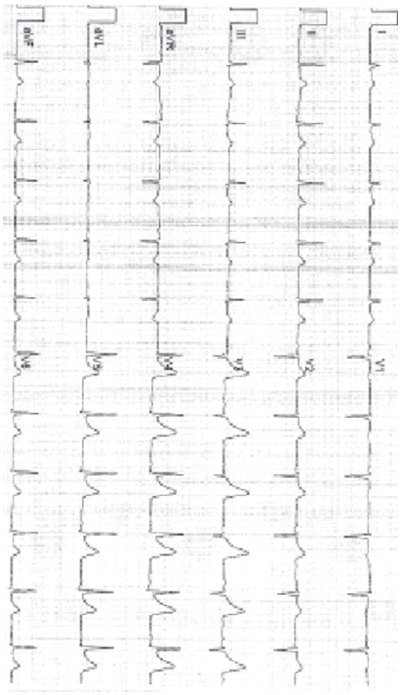
Introduction

Coronary heart disease in young patients is a big problem regarding the prognoses and the choice of treatment link to aetiology. We describe the case of a young woman without significant cardiovascular factor that had anterior myocardial infarction due to coronary thrombi of embolic origin. Echocardiogram reveals a patent foramen ovale associated with an atrial septal aneurysm.

Case report

A 27-year-old woman, para 2, who had an intrauterine device presented to us complaining of acute chest pain. She was diagnosed with acute coronary syndrome with persistent ST segment elevation and was in stable condition (Figure 1).

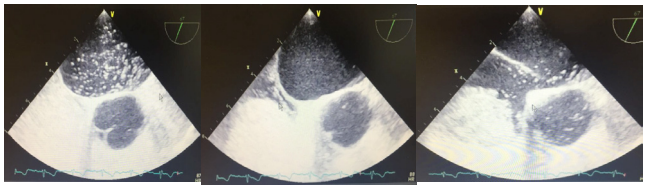
Figure 1: Electrocardiogram



Coronary angiography revealed a single-vascular lesion with acute occlusion of the second branch of the anterior distal anterior descending artery of thrombotic appearance associated with a thrombotic occlusion of the second branch of the first diagonal and a thrombotic occlusion of the very distal part of the first diagonal. It was not attempted thrombus apiration.

Echocardiography showed normal left ventricle size, not hypertrophied with segmental disorders of contractility, the ejection fraction of the left ventricle was estimated at 45-50% without visualized thrombus. Other cavities were of normal size. There was no valvular heart disease. The interventricular septum was intact. There was an atrial septal defect that motivated trans-oesophageal echocardiography; saline bubble contrast injection allowed to show a Patent Foramen Ovale (PFO) with significant passage without vasalva manoeuver associated with an Atrial Septal Aneurysm (ASA). No thrombus was visualized in cavities (Figure 2).

Figure 2: Trans oesophageal echocardiography



A second control coronarography was performed 2 days later after initiation of treatment with anticoagulant, inhibitor of the conversion enzyme and beta blocker; it showed a complete reversal of the coronary axes and the disappearance of the thrombi. As part of the aetiological assessment, the imaging and biological examinations were performed without particularity.

The presence of thrombus in a lesion-free coronary network made us strongly suspect an embolic process. We consider this condition as a presumed coronary

paradoxical embolism; there was non coagulation disorders detected in our patient.

She was put on an oral anticoagulation with apixaban, inhibitor of the conversion enzyme and beta blocker and benefit of a cardiac rehabilitation programme and therapeutic education. She recovered her myocardial function and we removed inhibitor of the conversion enzyme and beta blocker the following month. Given the prognostic and potential therapeutic implications, we proposed transcatheter closure of this atrial septal defect.

A few months later, she underwent amplatzer device implantation of a 35mm. A manual microbubble injection test was performed at the level of the inferior vena cava showing the absence of passage right - left, the existence of a device in place without visible residual shunt, procedure performed under local anaesthesia and under treatment with apixaban. She was discharged one day after the procedure without modification of the treatment. Apixaban will be removed later because of peri-procedural events hazard, guidelines are not clear regarding the duration or type of medication.

Discussion

Treatment of paradoxical embolisms through a PFO has been widely studied in the context of cerebrovascular accidents that constitute the most frequent clinical manifestation of presumed paradoxical embolism. The treatment is based on medical treatment to suppress the consequence or prevent recurrence and elimination of the pathway allowing paradoxical embolism. We extrapolated results in cases of non-cerebral embolic arterial accidents.

Discovering a PFO may be incidental or stroke related. To establish a link between PFO and stroke we can use the score Risk of Paradoxical Embolism (RoPE) (1). A score RoPE up or equal to 7 (maximum score 10) relates the stroke to the PFO and allows to have PFO closure for secondary prevention. Our patient was aged 27 years, with no history of hypertension, or diabetes, or stroke or TIA, or smoking had a score of 9. We therefore considered it a subject at risk of future embolism (1).

Various therapeutics are available in secondary prevention: antiplatelet agents; oral anticoagulants; surgical closure and percutaneous closure of the PFO. Option should be chosen by weighting the risk of the treatment itself against the expected benefit. Isolated PFO is a fairly common finding in practice and risk of recurrence in the absence of associated Atrial Septal Aneurysm (ASA) is identical to that of patients without PFO. PFO and ASA combination appears to be particularly susceptible to recurrence and is a subgroup for which secondary prevention is more aggressive than antiplatelet or oral anticoagulant (2).

In fact, ASA causes atrial dysfunction that may promote thrombus formation in the left atrium. Closure of PFO in patients with ASA is indicated (3). We chose apixaban regarding results of a meta-analysis proving that anticoagulation is superior to aspirin, however, the risk of haemorrhage due to long-term anticoagulation remains high (4).

PFO closure indications for secondary prevention of cryptogenic stroke are: stroke recurrence under anticoagulation therapy, contraindication or refusal of anticoagulant therapy or concomitant venous thrombo embolism with high risk of paradoxical embolism recurrence. In primary prevention only platypnea-Orthodeoxia syndrome is indicated (5). A recent study shows results of 3 surveys prove the benefit and superiority of PFO closure over medical therapy in secondary prevention of stroke (6).

Conclusion

Risk of recurrence persists until the underlying cause is treated and is higher in the case of ASA than in isolated PFO. More aggressive therapeutic strategy to reduce the risk of further embolism in active young patients without significant risk factor that have different prognoses than older patients could be PFO closure by amplatzer occluder.

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Case report

Postpartum Cerebral Venous Sinus Thrombosis: A Case Report

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Abstract

Background: Headache is a very common complaint in the postpartum period. It is even more common post spinal anaesthesia for Caesarean section delivery. The obstetrician will commonly prescribe analgesia to relieve the headache. If the headache is associated with elevation of blood pressure with or without convulsion, the obstetrician will almost always treat it as postpartum preeclampsia or eclampsia. Rare aetiology like sagittal sinus venous thrombosis should be kept in mind when managing such patients.
Case report: We present a case of a 24 year old lady P1+0,7 days post emergency Caesarean section due to non-reassuring fetal status (Outcome LFI,3300grams, doing well). She was admitted into Aga Khan University Hospital Nairobi (AKUHN) with a three day history of throbbing headaches in the frontal and parietal regions which were treated as post dural puncture headaches with oral paracetamol minus any relief. On the day of admission, she had witnessed generalized tonic clonic convulsion lasting around five minutes with post ictal confusion and drowsiness. Magnetic Resonance Angiography (MRA) revealed extensive cerebral venous sinus thrombosis in the sagittal, right transverse, sigmoid sinuses and proximal right internal jugular vein. The patient was initiated on heparinisation which was successful and discharged home after ten days.
Conclusion: Eclampsia is a very common cause of convulsions in the postpartum period but other causes, though rare like cerebral venous sinus thrombosis should be borne in mind.

Key words: Cerebral venous sinus thrombosis, Magnetic resonance venography, Headache, Convulsions, Postpartum

Introduction

Pregnancy is a thromboembolic condition. Most thromboembolic phenomenon related to pregnancy occur in the lower limb veins (1). Though rare, with an incidence of about 12 cases per 100,000 deliveries, cerebral venous sinus thrombosis which presents with a variety of symptoms from persistent headache to convulsions and coma is one of the thromboembolic phenomena in pregnancy (2-4). Most of the postpartum cerebral sinus thrombosis occurs within the first three weeks in puerperium. The frequency of sinuses affected are sagittal, transverse, sigmoid and cavernous sinuses respectively. Rarely the cortical and cerebellar veins may be affected (5-7). The obstetrician needs a high index of suspicion and good clinical acumen to diagnose this rare entity and not manage it as a case of postpartum eclampsia. We describe a case of cerebral venous sinus thrombosis in a 24 year old lady which was initially managed as eclampsia with post dural puncture headaches.

Case report

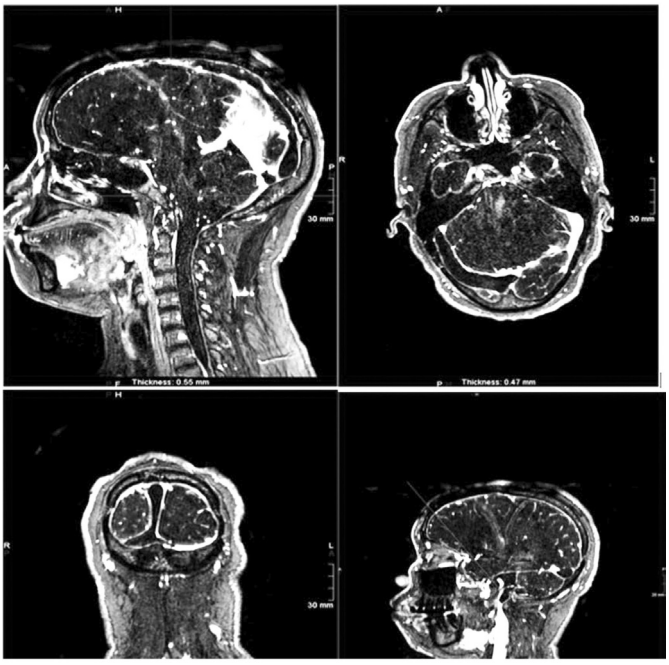
A 24 year old lady was admitted to the Aga Khan University Hospital High Dependency Unit with a three days history of throbbing headache in the frontal and parietal regions. On the third day of the presentation, she had a witnessed generalized tonic clonic convulsion with post ictal confusion. The patient was a para 1+0, seven days post emergency Caesarean section which was done due to non-reassuring fetal status. There was no antenatal history of high blood pressure or any family history of thrombotic event or stroke. She was not on any medications in the antenatal period apart from iron and folate supplements and in the

immediate postpartum period she was discharged home on painkillers. She never smoked cigarettes nor took alcohol in her life.

On physical examination, the patient was in good general condition, her RR was 26, blood pressure was 130/86, PR 71, temperature 36.6 with oxygen saturation of 96% on room air. Her Glasgow Coma Scale was 14/15 with a confused verbal response. She also had mild papilledema with no anisocoria. Babinski sign was absent. Her breasts were engorged and active, fundus was at sixteen weeks and firm with no tenderness. Pfennestiel incision scar was clean and dry with normal lochia loss. Her calves were warm and non-tender. There was no lower limb edema. The rest of the systems were essentially normal.

Her laboratory investigations were: RBS 3.9mmol/l, BGA was normal WBC 8.52, Hct 44%Hb 14900/ mm^3 with neutrophils of 71%, Plt 252,000/mm3, PCT 0.09, Ddimers 9928, malaria antigen test was negative, urinalysis was normal. Her routine biochemical tests including extended electrolytes were normal. Her coagulation profile, protein C and S and antiphospholipid antibodies were within normal. An emergency MRV was ordered which revealed extensive venous sinus thrombosis involving the sagittal, right transverse, sigmoid sinuses and proximal right internal jugular vein with a small extension to the left transverse sinus (Figure 1).

Figure 1: Sagittal, axial and coronal sections showing extensive cerebral venous sinus thrombosis



Subcutaneous enoxaparin 80mg twice daily was immediately started which she used for 7 days and later switched to warfarin 5mgs once daily for one month. She also had an epidural blood patch placed for controlling her post dural puncture headaches which seemed not to get better even with opioids. The other supportive medications like anticonvulsants and other painkillers were also given. The patient got better and was allowed home on warfarin 5mgs daily, anticonvulsants and painkillers. She was followed up in the neurology clinic and warfarin was stopped after one month.

Discussion

Cerebral venous sinus thrombosis with its recognized and known causes is very rare. Though very difficult to diagnose in resource poor settings where radiological investigative ability may be lacking, clinical acumen should come in handy. When recognized early, there is a very high potential for full recovery but late diagnosis has a very high mortality. Headache is the most common presentation and the sagittal sinus is the most affected (8-10). The patient may present with focal or generalized convulsions with a higher incidence in puerperium and this makes the diagnosis to be easily confused with eclampsia especially when the presentation is mild (11,12). CT scan angiography misses almost a quarter of the cases, MRV is the gold standard radiological investigation for cerebral venous sinus thrombosis (13-15). Treatment of cerebral venous sinus thrombosis is by coagulation and low molecular weight heparin; enoxaparin has been accepted as a safe medication for treatment. The team managing the patient should be aware of the risk of haemorrhage when on the enoxaparin and any deterioration in the Glasgow coma scale of the patient while on heparinisation should warrant a repeat imaging to rule out a haemorrhagic infarct and the drug should be immediately stopped if haemorrhage is confirmed. The anticoagulation therapy should be continued for a period of six months unless the patient has thrombophilia (3,9,12,16).

Conclusion

If recognized early, postpartum cerebral sinus thrombosis is treatable and patients can fully recover. The obstetrician and the emergency care physician need to be aware of this rare cause of postpartum headache and convulsions and act early. High index of suspicion and good clinical acumen with availability of good radiological investigation will help pick these cases which have almost always been managed as cases of postpartum eclampsia. Late diagnosis leads to morbidity and mortality which can be easily avoided.

Conflicts of interest: No conflicts declared.

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