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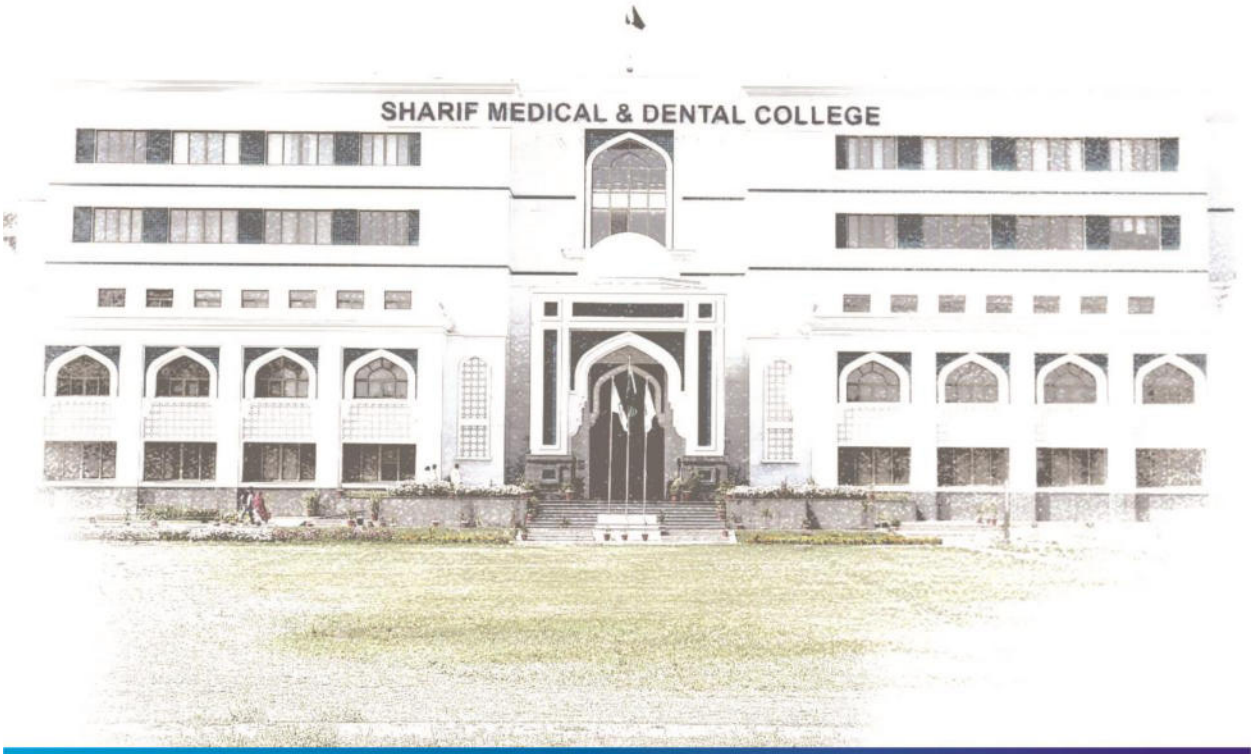

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Editorial

Measles - A Global Problem

Emran Roshan

Measles, a vaccine-preventable disease, is extremely contagious and it spreads via airborne transmission. A susceptible person who has face-to-face contact with an infected person has a 90% likelihood of developing the disease.[1,2] Measles is still common in many parts of the world, particularly in countries with developing economies. Approximately 20 million cases are estimated to occur globally each year, with 164,000 deaths; most fatalities occur in children under 5 years of age.[3]

Measles virus is single stranded RNA virus. Humans are the only host. Portal of entry is conjunctivae and upper respiratory tract. Patients are infectious from three days before to up to six days after onset of rash. Mostly diagnosis is clinical but in absence of outbreak serologic confirmation is recommended by identification of IgM in serum 1-2 days after onset of rash and a fourfold rise in the level of serum IgG.[4]

Measles can lead to life-threatening complications. Measles virus causes immunosuppression leading to severe bacterial and viral infections along with activation of latent tuberculosis.[6] Post measles pneumonia is most the common cause of death while acute otitis media is the most common complication. Subacute sclerosing panencephalitis «(SSPE) is a chronic complication with fatal outcome. The slow virus infection results in inflammation and death of brain cells leading to irreversible neurodegenerative process. Clinical manifestation of SSPE begins 7-13 years after primary measles infection. Progressive loss of brain matter ultimately leads to death. Vomiting, diarrhea, croup, tracheitis, bronchiolitis, febrile seizures are other complications which can occur. Complications of measles are common in patients younger than 5 years of age and more than 20 years of age and in those who are malnourished.[5,6]

Measles vaccine has changed epidemiology of the disease. After introduction of two dose vaccine policy and more intensive immunization strategies, the attack rate of measles fell from 313 cases per 100,000 population in 1956-1960 to 1.3 cases per 100,000 in 1982-1988 in the United States. In spite of the vaccination, measles outbreaks continue to occur which may be due to vaccine failure in school going children, low coverage of preschool age children and rapid waning of maternal antibodies in infants born to mothers who had never experienced wild type measles.

In Europe, there were 21315 cases of measles and 35 deaths in 2017, a 400% increase as compared to previous year when there was a record low cases (5273) according to WHO. Large outbreaks of measles have affected 15 of the 53 countries in the WHO European region, with the highest numbers seen in Romania (5562) and Italy (5006) and Ukraine (4767).[7]

On the verge of a measles catastrophe, the country is facing an increasing number of reported cases compared to 2016. The numbers reveal that Pakistan not only experienced a significantly higher number of cases than the entire region but that cases rose by more than 100 percent in 2017, compared to previous year. According to the Measles-Rubella Bulletin, the data analysis on the region reports 6,494 cases in 2017, while in 2016 the reported cases were 2,845.[9]

According to WHO standards, 95% vaccine coverage is necessary to avert an outbreak as the disease is highly infectious. Even reaching 80% coverage will avert large scale outbreaks. Except for Punjab and Azad Kashmir all other provinces report 56% or less coverage.[10] There are multiple causes of vaccine failure in Pakistan like paucity of vaccination centers, improper vaccination storage facilities, inadequate staff, corruption and least interest of parents in getting their child vaccinated.[11]

Only through vaccination measles can be prevented. It is recommended that all children should receive 2 doses of vaccine, one at age of 9 months and the other at age of 15 months.[12]

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Original Article

Frequency of Occult Hepatitis B in Hemodialysis Patients

Aqsa Aslam, Maria Aslam, Qurat-ul-Ain

ABSTRACT

Objective: To detect the frequency of occult hepatitis B among hemodialysis patients of Shaikh Zayed Hospital, Lahore.

Methodology: It was a cross-sectional descriptive study. Two hundred HBsAg negative hemodialysis patients were included in the study. Consecutive sampling technique was used. The blood samples of hemodialysis patients were taken from Shaikh Zayed Hospital, Lahore . Hepatitis B surface antigen (HBsAg) was performed by ELISA kit. The real-time polymerase chain reaction (PCR) was performed to detect HBV DNA in serum samples of 200 HBsAg negative hemodialysis patients. The data was analyzed by using SPSS version 21.

Results: The mean age of the study population was 47.05±14.33 years. One twenty one (60.5%) patients were males and 79 (39.5%) were females. The mean duration of hemodialysis was 48.21±42.21 months. In our study, 96.5% (193/200) of the patients were vaccinated and 3.5% (7/200) were unvaccinated. The frequency of occult hepatitis B was zero.

Conclusion: The frequency of occult hepatitis B was zero in hemodialysis patients. As most of the patients were vaccinated, it was concluded from our study that the prevalence of occult hepatitis B is low in vaccinated hemodialysis patients.

Keywords: *Occult hepatitis B. Hemodialysis patients. HBsAg. HBV DNA.*

INTRODUCTION

Occult hepatitis B (OHB) is a condition in which hepatitis B virus DNA is present in the liver and serum of hepatitis B surface antigen (HBsAg) negative individuals. The viral DNA level in the serum is low, usually less than 104 copies/ml.[1] It can be transmitted through hemodialysis, organ transplantation and blood transfusion.[2,3] Unidentified occult hepatitis B in hemodialysis patients is a potential source of infection for other patients. These patients are highly susceptible to acquire hepatitis B especially in setups where the recommended infection control measures are not strictly followed.[1]

Occult hepatitis B can develop into active hepatitis B infection by viral replication as a result of immunological disorders or immunosuppressive therapies.[4] It can progress to cirrhosis and even hepatocellular carcinoma.[2,3] Hepatitis B virus DNA detection in liver biopsy specimen is the most reliable method to diagnose occult hepatitis B. However, it is contraindicated in patients of hemodialysis (HD) so the diagnosis relies on HBV DNA detection in the serum sample.[5,6]

The frequency of occult hepatitis B depends on endemicity of hepatitis B in that area and sensitivity of the HBsAg and HBV DNA kits.[7] The detection rate of occult hepatitis in hemodialysis patients was 3.7% in North America,[8] 4.9% in India,[9] 0 to 26.6% in Italy [10,3] and 2.7% to 12.4% in Turkey.[11,12]

Hepatitis B is common in Pakistan. There is a high risk to acquire and transmit HBV infection among HD patients by various means. The hepatitis B prevalence in hemodialysis patients was 10.2% and 12.4% according to studies conducted in Karachi and Islamabad respectively[13,14], whereas in normal population, HBsAg positivity was 2.5%.[15] In all these studies, patients were tested for HBsAg but polymerase chain reaction (PCR) was not performed to detect HBV DNA. This study was planned to detect HBV DNA by PCR in the serum samples of hemodialysis patients who were screened negative for HBsAg. A higher frequency of occult hepatitis B was expected in these patients. These patients, as being previously undiagnosed, are a potential source of infection. Diagnosing these patients will help us in implementing better protective measures in hemodialysis patients in order to reduce its further spread.

METHODOLOGY

It was a cross-sectional descriptive study. Two hundred HBsAg negative hemodialysis patients were included in the study. Consecutive sampling technique was used. Informed consent was obtained from the patients. Personal history and other required information was documented on a Proforma sheet for each patient. The research study was approved by the Institutional Review Board (IRB) of Postgraduate Medical Institute, Shaikh Zayed Hospital, Lahore. The blood samples of hemodialysis patients were taken from Shaikh Zayed

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Hospital, Lahore. The samples were centrifuged at 5000 rpm for 5 minutes and serum was separated. HBsAg was performed by ELISA kit manufactured by CTK Biotech diagnostics. The serum samples of 200 HBsAg negative patients were included in the study. Polymerase chain reaction was performed in serum samples to diagnose occult hepatitis B by Sustaaq USA kit.

STATISTICAL ANALYSIS

The data was analyzed by using the statistical package of social sciences (SPSS) version 21. Age and duration of hemodialysis were described by using mean ± SD. Gender, cause of ESRD, vaccination status of patients and PCR results were presented by using frequency and percentages. A p-value < 0.05 was considered as statistically significant.

RESULTS

The mean age of hemodialysis patients was 47.05 ±14.33 years. One twenty one (60.5%) patients were males and 79 (39.5%) were females. The age distribution of the patients is shown in figure1.

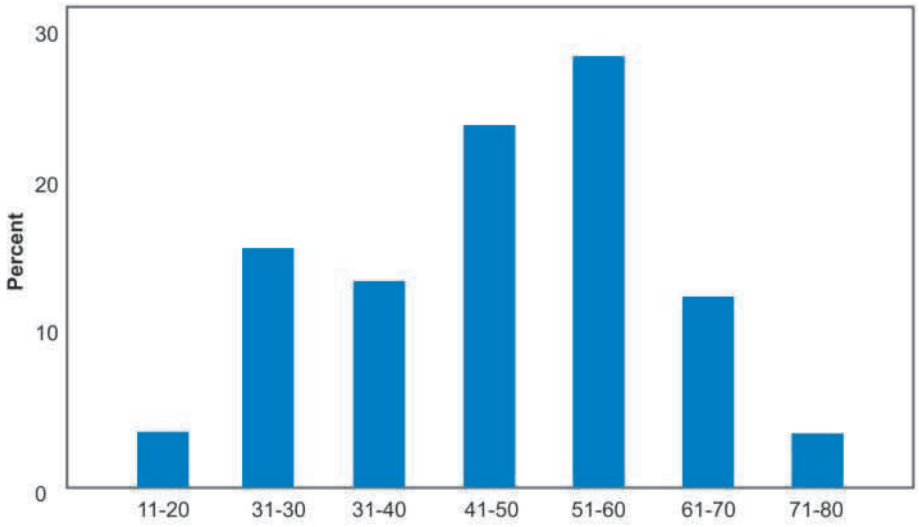
The mean duration of hemodialysis was 48.21±42.21 months. The minimum duration of hemodialysis was 3 months and the maximum duration was 264 months (22 years). The common causes of the end-stage renal disease was hypertension (HTN) accounting for 42% of the cases followed by both HTN and diabetes mellitus (DM) in 27% of the patients. Diabetes mellitus alone was the cause of ESRD in 6.5% cases. Other causes are glomerulonephritis, nephrolithiasis/obstructive nephropathy, nephritic syndrome, hydronephrosis, polycystic kidney disease and congenital one kidney. The cause was unknown in about 11.5% of the patients. In our study, 96.5% (193/200) of the patients were vaccinated and 3.5% (7/200) were unvaccinated. The frequency of occult hepatitis B was zero. The 4 quantitative standards, negative template control, a known hepatitis B positive serum sample and 200 study samples were run on the Rotor-Gene instrument. HBV DNA was not detected in any study sample.

DISCUSSION

The frequency of occult hepatitis B ranges from 0 to 58% worldwide depending on the endemicity of hepatitis B in that region.[16] It not only differs from country to country but also among different regions of the same country. In a study conducted in Italy, the prevalence of occult hepatitis B was 26.6% whereas in another study the prevalence of occult hepatitis B was 0 in Italy. It may be attributed to the difference in prevalence of hepatitis B in these areas.[10,3]

Our results showed that the frequency of occult hepatitis B was zero in hemoodialysis patients. Similar results were found in other studies. The prevalence of occult hepatitis B in hemodialysis patients was 1.25% in Turkey (Ankara). Eighty hemodialysis patients with negative HBsAg were enrolled. The serum sample of only 1 patient was positive for HBV DNA.[16] In another study carried out in Turkey (Diyarbakir), the prevalence of occult hepatitis B was 0. Out of 50 HBsAg negative hemodialysis patients, HBV DNA was not detected in any patient.[17] In contrast to our study, the prevalence of occult hepatitis B was high in hemodialysis patients in other studies. The prevalence of occult hepatitis B was 58% in Spain and 20.4% in another study in Greece.[8]

Occult hepatitis B is much more common in unvaccinated hemodialysis patients.[5] In our study, 96.5% (193/200) of the patients were vaccinated and 3.5% (7/200) were unvaccinated. In a study by Ersoy in Turkey, 73.75% (59/80) patients were vaccinated and



Figher 1: Age distribution of the study subjects.

26.25% (21/80) were unvaccinated.[16] According to a study in Spain, the prevalence of OHD was found to be 58%. In this study, 33 HD patients and 24 dialysis staff members were included. All of the study participants were HBsAg negative. Only 3 HD patients and 16 staff members were vaccinated whereas 8 staff members had a history of previous HBV infection. HBV DNA was present in 19 (58%) HD patients and 8 staff members (who had past HBV infection). The reason behind this higher prevalence of occult hepatitis B may rely on the enrollment of high risk participants in the study (those with a history of previous hepatitis B or who were anti-HBc positive). Secondly, vaccination decreases the rate of transmission of occult hepatitis B. In this study, only 3 HD patients were vaccinated.[8]

The type of sample used for PCR also affects the detection of occult hepatitis B. The detection rate is greater in peripheral blood mononuclear cells (PBMCs) as compared to the serum sample. In our study, serum samples were used for detection of HBV DNA. In a study by Oesterreicher et al. PCR was performed in both the serum and PBMCs of 67 HBsAg hemodialysis patients. Six patients (8.9%) had HBV DNA in their PMBCs whereas none of them had detectable HBV DNA in their serum.[5]

The level of viremia varies in occult hepatitis B and can be a factor altering the frequency of occult hepatitis B. According to a study in Austria, PCR was done on 82 serum samples and 16 liver specimens. These patients were negative for HBsAg and had chronic hepatitis C. Hepatitis B virus DNA was present in 22% serum samples and 19% liver specimens. The serum samples were again collected from these patients and HBV DNA was analyzed. The results found were inconsistent. The previously positive HBV DNA samples showed negative results and vice versa. These results suggest that the level of viremia fluctuates during the disease.[5]

The rate of HBV DNA detection is also affected by the sensitivity of the assays used. In a study carried out in Korea, 98 HD patients were included. Four (4.1%) patients had positive HBsAg and they were excluded. The HBsAg negative patients were tested for HBV DNA by using two different techniques of PCR. HBV DNA was detected in 3 (3.2%) patients by Cobas Amplicor HBV monitor test and 1 (1.1%) patient by Taqman real-time PCR kit.[18]

CONCLUSION

The frequency of occult hepatitis B was zero in hemodialysis patients. As most of the patients were vaccinated, it was concluded from our study that the prevalence of occult hepatitis B is low in vaccinated hemodialysis patients. Occult hepatitis B is transmissible among HD patients but we do not recommend routine screening of HD patients for HBV DNA.

LIMITATIONS OF THE STUDY

- Our study population included patients from a single hemodialysis unit of Shaikh Zayed Hospital. So, our results cannot predict the frequency of occult hepatitis B in other hemodialysis units of the country.

- HBV DNA testing was done on serum samples in contrast to peripheral blood mononuclear cells and liver. This may have underestimated the true frequency of occult hepatitis B.

RECOMMENDATIONS

- The study participants should be enrolled from multiple hemodialysis units.

- The peripheral blood mononuclear cells and liver specimens (if possible) should be analyzed for detecting HBV DNA along with the serum samples.

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Original Article

Knowledge and Practices about Breast Cancer among Female Paramedical Staff at Sharif Medical City Hospital (SMCH), Lahore.

Laila Afzal, Muhammad Moaaz, Lubna Ayub, Namra Zahoor, Amna Iqbal Butt, Qurat-ul-Ain, Muhammad Shahid Iqbal

ABSTRACT

Objective: To assess knowledge and practices about breast cancer among paramedical staff at SMCH, Lahore.

Methodology: It was a cross-sectional descriptive study in which 100 female paramedical staff personnel of SMCH were interviewed. The data was collected through a questionnaire which was analyzed by computer software SPSS (Statistical Package for Social Science) version 23.0.

Results: Among 100 respondents, female paramedics who had knowledge about breast cancer as the most common cancer in women were about 93%. Sixty six (66%) respondents had knowledge about the association of breast cancer with family history. Female paramedics who knew that breast self-examination (BSE) is useful in early diagnosis of cancer were 96%. They practiced BSE once in a month routinely. Respondents who had awareness about the first presentation of breast cancer as a painless lump in the breast were 94%. Those who never went for clinical breast examination were 72%. According to overall scoring of knowledge section, 71% had good knowledge about breast cancer, 11% had fair and 18% had no/poor knowledge.

Conclusion: The overall level of knowledge about breast cancer occurrence, signs and symptoms and early diagnosis among female paramedics of Sharif Medical City Hospital was found to be up to the mark but their level of awareness regarding practices leading to early diagnosis of breast cancer still needs attention.

Keywords: *Breast cancer. Knowledge and practices about breast cancer. Breast self-examination (BSE).*

INTRODUCTION

Cancers, as non-communicable diseases, are among leading causes of death worldwide. Almost all breast cancers arise from epithelial cells in the breast, usually beginning in the inner lining of milk ducts or lobules. It is a malignant neoplasm that has the ability to metastasize to other parts of the body. According to a survey, nearly 1 out of every 9 women suffer from the breast cancer.[1] According to World Health Organization (WHO), it accounts for 10% of all the cancers diagnosed in the world and 22% of all new cancers in 2000 women. In the 21st century, one million cases were reported.[2] In Asian countries, Pakistan has the highest incidence rate of breast cancer.[3]

Breast cancer is the 2nd leading cause of death in Pakistan.[4] According to a research, the incidence of breast cancer in Pakistan is 2.5 times more than other Asian countries like India.[5] Women with breast cancer over the age of 50 are about 77%.[6] There are many reasons for its widespread presentation in Pakistan. In our healthcare system, there is no setup for data collection and recording of cases, lack of proper healthcare setup and illiteracy among women. Family history, drinking alcohol, obesity and aversion to breastfeeding are also thought to be among the major causes. Other factors that increase the chances of breast cancer are long menstrual history, nulliparity or having the first child after the age of 30, postmenopausal hormone replacement therapy and radiation exposure.[6] Reports from Western Europe and North America stated that there is a decrease in death rate from breast cancer due to use of screening methods for detection of early disease.[7] Developing countries should arrange programs for awareness of females.[8] It is reported that the most common symptom of breast cancer is a painless lump so breast self-examination (BSE) is the first step for early diagnosis. Most of the breast cancer patients in developing countries present at terminal stages resulting in poor response to treatment. Early diagnosis of cancer affects the chances of patient's recovery and long term survival.[9,10]

Many women die due to this lethal disease. The aim of this study was to reveal the issue of breast cancer awareness although the exact cause and treatment of this malignancy is still being studied. So, in the light of above mentioned factors, it was pertinent to conduct the study.

METHODOLOGY

It was a descriptive cross-sectional study conducted at Sharif Medical City Hospital. Lahore. Non-probability, convenient sampling technique was applied. The sample size was calculated to be 100 using statistical software. All married and unmarried female paramedics above age 15, not currently diagnosed with breast cancer were included in the study. All female paramedics currently diagnosed with breast cancer and those who refused to participate in the study were

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excluded.

Data was collected using a semi-structured questionnaire which was finalized after pretesting. Female paramedics were interviewed by researcher and responses were noted on the questionnaire. Scoring was done for knowledge section where each question had a score of 1 for yes response and zero for no/don't know response. Total score for knowledge section was 17. Those scoring 70% or more were considered having good knowledge, between 40-70% as fair knowledge and less than 40% as poor knowledge.

STATISTICAL ANALYSIS

Data was analyzed in computer software SPSS (Statistical Package for Social Science) version 23.0. Frequencies and percentages were calculated and presented in tables.

RESULTS

Out of 100 respondents, the majority (72%) were in 15-25 years age group. Forty four (44%) were nurses. The majority (79%) were unmarried and forty two (42%) were educated up to intermediate level (Table 1). Results showed that 93% of female paramedics had knowledge about breast cancer as a frequently occurring cancer in women of Pakistan while 41% were aware about the occurrence of breast cancer more commonly in old age. Sixty six (66%) respondents had the knowledge about association of breast cancer with family history while 26% of the population believed evil spirits to be the cause of disease. Majority of the respondents (98%) were aware that early diagnosis improves the outcome of disease and 96% had knowledge of breast self-examination (BSE). Major source of knowledge about breast self-examination was a doctor (50%) while only 17% got information from electronic media.

Majority of the respondents had knowledge about signs and symptoms of breast cancer, about 94% were aware of presentation as a painless lump in the breast. Eighty seven (87%) were aware about breast self-examination as an early diagnostic technique. According to overall scoring of knowledge section, 71% had good knowledge about breast cancer, 11% had fair and 18% had no/poor knowledge.

DISCUSSION

In our study, it was encouraging to know that 90% of respondents had knowledge about breast cancer as the most common cancer in women. Similar results were found in a study conducted by Noreen et al. in which most of the non-medical (73%) and medical (80%) students were aware of the fact that breast cancer is among the most prevalent cancers in women of Pakistan.[11] Similarly, 60% of respondents claimed breast cancer as a disease with a hereditary basis which is in

Table 1: Socio-demographic characteristics of respondents

Characteristics Age (in years)	Frequency	Percentage
15-20	36	36.0
21-25	36	36.0
26-30	24	24.0
31-35	2	2.0
36-40	1	1.0
41-45	1	1.0
Working Status		
Staff nurse	18	18.0
Charge nurse	18	18.0
Student	44	44.0
Teacher	5	5.0
Helper	15	15.0
Educational Status		
Matric	22	22.0
Intermediate	42	42.0
Above Intermediate	36	36.0
Marital status		
Married	21	21.0
Unmarried	79	79.0

Table:2 Responses about different aspects of knowledge about breast cancer

Different aspects of knowledge	Poor knowledge	Fair knowledge	Good knowledge
Causes of breast cancer	07(7%)	27(27%)	66(66%)
Signs and symptoms of breast cancer	26(26%)	06(6%)	68(68%)
Diagnostic techniques of breast cancer	13(13%)	08(8%)	79(79%)
Early diagnosis improving the outcome	02(2%)	0(0%)	98(98%)

contrast to another study in which 85% medical students were sure that family history makes a woman more vulnerable to breast cancer.[11]

It was distressing to know that 26% of the respondents blamed evil spirits as a cause of breast cancer in a study conducted by Okobia et al.[12] In our study, 40% of the participants claimed evil spirits to be the cause of breast cancer which seems to be ridiculous as the modern research has totally negated these baseless and futile concepts. Early diagnosis of any disease always improves the outcome, it was apparent from the study that 98% of the respondents had knowledge of the better outcome of breast cancer if diagnosed at very initial stages leading to decreased mortality and morbidity.

Breast self-examination (BSE) is one of the very popular and potent methods for early diagnosis. It was very encouraging that 96% of respondents were having knowledge of breast self-examination which is in contrast to study conducted by Okobia et al. in which only 43.2% of study participants admitted to carrying out the procedure in the past year.[12]

Our results showed that only 28% of participants had clinical breast examination (CBE) in past year. Similar results were found in other studies.[11.12]

The signs and symptoms are of paramount importance for the diagnosis and subsequent treatment of a disease. Majority of respondents (94%) had knowledge about the lump in the breast as the first presentation of disease which was in line with the study conducted by Noreen et al. According to them, 90% students were familiar with the fact that the presence of a lump in breast tissue can be an early warning sign.[11] As we know that discharge from the breast is also early signs of breast cancer but only 48% of respondents were aware of this. Similarly, 74% of respondents claimed the discoloration/dimpling of the breast as one of the early signs.

It was distressing to know that only 17% respondents got knowledge of breast self-examination from television. Another study conducted in Punjab showed that television and school/college education were most cited sources of information regarding breast cancer. Similarly, 50% of respondents got knowledge from a doctor which need further strengthening regarding this important issue.

CONCLUSION

The overall level of knowledge about breast cancer occurrence, signs and symptoms and early diagnosis among female paramedics of Sharif Medical City Hospital was found to be upto the mark but their level of awareness regarding practices leading to early diagnosis of breast cancer still needs attention.

Role of media in imparting knowledge about practices regarding early diagnosis of breast cancer was deficient as most of the respondents obtained this knowledge from a doctor or other organizations. Social and cultural barriers as shown by the discomfort of the respondents in breast examination by a male doctor also play their role to increase the burden of disease.

RECOMMENDATIONS

- Health education should be channeled through women friendly agencies/organizations such as hospital, antenatal and postnatal clinics, religious organizations and feminist organizations.
- Awareness seminars especially family awareness programs must be conducted not only to educate women but also involving male members to provide necessary economical and psychological support in coping with the disease.
- The education regarding monthly breast self-examination with accurate technique and daily observation of any visual changes should be provided through pamphlets, brochures, talks and publications for the people at all healthcare institutes.
- Routine breast cancer screening programs must be designed.
- Role of media, both print and electronic needs to be enhanced in spreading awareness about breast cancer prevention and diagnosis at early stages.
- Due to religious and cultural constraints, most of the women refuse or feel discomfort to visit male doctors for clinical breast examination so more female doctors must be made available in the field to cope with this difficulty.

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Original Article

Vitamin B12 Deficiency in Patients with Type 2 Diabetes Mellitus Taking Metformin

Maria Aslam, Khawar Naeem Satti, Aqsa Aslam

ABSTRACT

Objective: To determine the frequency of vitamin B12 deficiency in type 2 diabetics taking metformin.

Methodology: It was a cross-sectional study conducted at Pathology Department of Sharif Medical City Hospital, Lahore. The study was approved by the ethical committee of the hospital. A total of 100 patients with type 2 diabetes mellitus taking metformin for more than two years were included in the study. Informed consent was obtained from all patients and history regarding medicine intake and any other illness was taken. Serum vitamin B12 levels of all study subjects were measured.

Results:The study included 40 males and 60 females. The mean age of the patients was 53±5 years. The duration of metformin use was between 2-9 years with a mean value of 5.1± 2 years. The daily dose of metformin was noted in all patients and its mean value was 1490 ±257 mg/day. Mean level of serum vitamin B12 was 161±24 pg/mL and ranges from 120 pg/mL to 220 pg/mL. Level of serum vitamin B12 was normal in 5 (10%) patients and low in 45 (90%) patients. Mean level of vitamin B12 in patients taking metformin for 2-5 years was 160pg/mL whereas in patients on metformin for 6-9 years mean value was 145pg/mL. There was a significant association between serum vitamin B12 level and duration of metformin intake.

Conclusion: Vitamin B12 deficiency occurs in patients with type 2 diabetes treated with metformin for a longer duration.

Keywords: *Vitamin B12. Diabetes mellitus. Metformin. Type 2 diabetes.*

INTRODUCTION

The prevalence of diabetes mellitus is increasing worldwide. Management of diabetes mellitus involves lifestyle modification, oral hypoglycemics and insulin. Lifestyle modification and metformin are recommended as the first line treatment for type 2 diabetics. Metformin which belongs to a biguanide group is the most commonly given oral hypoglycemic drug in type 2 diabetes.[1] It reduces insulin resistance in the body and risk of development of macrovascular complications of diabetes. It is generally a well tolerated drug with few side effects like abdominal discomfort, nausea, diarrhea and lactic acidosis. In addition, prolonged metformin use causes vitamin B12 deficiency.[2-4]

Vitamin B12 binds with intrinsic factor and absorption of the vitamin B12-intrinsic factor complex occurs through cubulin receptors present in the ileum. The mechanism by which patients taking metformin develop vitamin B12 deficiency is still not clear. The proposed mechanisms include alteration in intestinal motility, bacterial overgrowth in the intestine, interaction with cubulin receptors and decreased vitamin B12 absorption. Use of proton pump inhibitors or H2-receptor antagonists can also cause vitamin B12 deficiency. According to different studies, the most likely cause of metformin induced vitamin B12 deficiency is the alteration in calcium dependent vitamin B12-intrinsic factor complex uptake by cubulin receptors present in ileum.[5-8]

Vitamin B12 has a major role in the synthesis of DNA, haemopoiesis and neurological function. Clinical manifestations of vitamin B12 deficiency include megaloblastic anemia and neurological symptoms like paresthesias, numbness and tingling sensation in hands and feet. It can also cause sub-acute combined degeneration of the spinal cord in which degeneration of the posterior and lateral columns of the spinal cord occurs.[9] These symptoms can be prevented by early diagnosis of vitamin B12 deficiency and appropriate B12 supplementation.[3] Vitamin B12 deficiency is also associated with increased levels of homocysteine in the body. Elevated homocysteine levels have toxic effects on neurons and vascular endothelium and in turn are associated with an increased risk of cardiovascular disease.[1] Vitamin B12 deficiency is diagnosed by detecting serum vitamin B12 levels.[5]

The prevalence of diabetes and its complications is high in Pakistan. Metformin is the most commonly used oral hypoglycemic drug for the treatment of type 2 diabetes. So, diagnosis of vitamin B12 deficiency in type 2 diabetics taking metformin will help in the prevention of its complications.

METHODOLOGY

This was a cross-sectional study conducted at Pathology Department of Sharif Medical City hospital,

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Lahore. The study was approved by the ethical committee of the hospital. A total of 100 patients with type 2 diabetes mellitus taking metformin for more than two years were included in the study by probability random sampling technique. Informed consent was obtained from all patients and history regarding medicine intake and any other illness was taken. The blood sample of all patients was drawn by aseptic measures. Serum vitamin B12 level was performed on all subjects by chemiluminescence method. The normal range of serum vitamin B12 level was 187- 883 pg/mL. Exclusion criteria included patients with newly diagnosed type 2 diabetes, pernicious anemia, pregnant women, type 1 diabetes, decreased renal function (serum creatinine levels >1.7 mg/dL for men and >1.5 mg/dL for women), prior vitamin B12 injections, gastrectomy, colectomy, inflammatory bowel disease and vegetarianism. Patients were also excluded if they had any severe medical illness such as sepsis, severe infection, malignancy, liver cirrhosis, heart failure or renal failure.

STATISTICAL ANALYSIS

The data was analyzed using SPSS 23.0. The quantitative variables were expressed as mean ± SD whereas the qualitative variables were reported as frequency and percentage. A p-value of $\leqslant 0.05$ was considered as statistical significance.

RESULTS

The study included 40 males and 60 females. The mean age of the patients was 53±5 years. The duration of metformin use was between 2-9 years with a mean value of 5.1±2 years. The daily dose of metformin was noted in all patients and its mean value was 1490±257 mg/day. Mean level of serum vitamin B12 was 161±24 pg/mL and ranges from 120 pg/mL to 220 pg/mL. Level of serum vitamin B12 was normal in 5 (10%) patients and low in 45 (90%) patients. Serum vitamin B12 levels of study subjects were compared on the basis of duration of metformin intake. Mean level of vitamin B12 in patients taking metformin for 2-5 years was 160pg/mL whereas in patients on metformin for 6-9 years mean value was 145pg/mL. A significant difference was found when mean levels of vitamin B12 in patients taking metformin for 2-5 years was compared with mean value in patients on metformin for 6-9 years. No significant association was found between dose of metformin and serum vitamin B12 levels.

DISCUSSION

The frequency of diabetes mellitus has increased significantly in the last three decades worldwide especially in Asia and is the ninth cause of death. Globally about 1 in 11 persons have diabetes mellitus and 90% of individuals have type 2 diabetes mellitus. The main factors predisposing to diabetes are genetic predisposition, unhealthy diet and sedentary lifestyle.[10]

Vitamin B12 is an important water soluble micronutrient which is essential to maintain haemopoietic, neurological and cardiovascular function. Different studies have shown that both the biochemical and clinical vitamin B12 deficiency are common in type 2 diabetic patients. The most important factor leading to vitamin B12 deficiency in type 2 diabetic patients is metformin use. The prevalence of vitamin B12 deficiency range from 5.8% to 33% in type 2 diabetic patients taking metformin.[9]

Twenty male and 30 female patients with the mean age of 53±5 years were included in this study. Serum vitamin B12 levels in type 2 diabetes did not show any significant association with age and gender. Similar

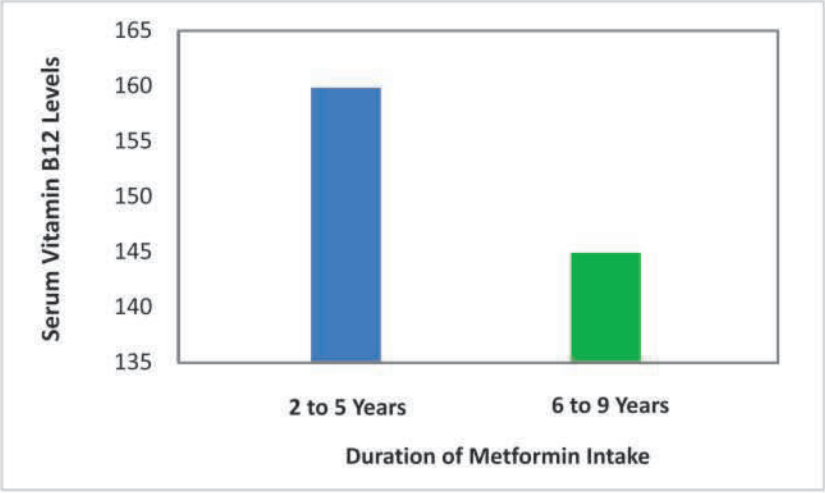

Figure 1: Association of serum vitamin B12 level with duration of metformin intake

results were observed in other studies.[10,14]

Our results showed that 45 (90%) patients developed vitamin B12 deficiency after metformin use. Comparable results were found in other studies.[8,15] Another study found that patients with type 2 diabetes on long-term use of metformin had lower levels of serum cobalamin and holotranscobalamin.[11]

A study conducted by Reinstatler et al. showed a strong association between metformin intake and decreased serum B12 levels in type 2 diabetics. They observed that intake of vitamin B12 in the form of multivitamins was associated with improvement in vitamin B12 levels.[12]

In this study, we found a significant association between duration of metformin intake and vitamin B12 deficiency. Serum vitamin B12 levels were more decreased in patients taking metformin for more than 5 years. Similar results were reported in another study which showed that use of metformin for more than 4 years increases the risk of vitamin B12 deficiency.[8] Another study indicated that duration of metformin is strongly associated with risk of vitamin B12 deficiency.[9]

Our results showed no association between dose of metformin and vitamin B12 levels. This is in contrast to another study which indicated a strong association between dose of metformin and serum vitamin B12 level.[8,9]

A study was conducted in Korea to evaluate the relationship between the duration of metformin use and vitamin B12 deficiency. It showed a negative correlation of vitamin B12 deficiency with the daily dose of metformin and the duration of metformin use.[13]

In another study, effects of dose and duration of metformin use on B12 levels in diabetics taking metformin were observed. Effects of dose of metformin on B12 deficiency among patients taking less than 1500 mg and more than 1500 mg were noted. According to them daily dose of metformin had an inverse correlation with vitamin B12 levels. Serum vitamin B12 levels of type 2 diabetic patients taking metformin for less than 24 months were compared with the patients on metformin for more than 24 months. Duration of metformin intake showed statistically significant association with B12 deficiency.[12,16] Vitamin B12 levels start decreasing as early as the 4th months after using metformin. However, clinical manifestations of vitamin B12 deficiency occur after 5–10 years due to vitamin B12 stores in the liver.[9]

There is a limitation to this study that other indicators of vitamin B12 deficiency like homocysteine or methylmalonic acid were not done due to financial constraints.

CONCLUSION

Vitamin B12 deficiency occurs in patients with type 2 diabetes treated with metformin with duration of more than 2 years.

RECOMMENDATIONS

Patients with type 2 diabetes taking metformin should be screened for vitamin B12 levels regularly to prevent the complications associated with vitamin B12 deficiency.

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Original Article

Relationship of Glasgow Coma Scale and CT Scan Brain findings in Head Trauma Patients of Different Age groups

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ABSTRACT

Objective: To determine the relationship between GCS score and CT scan brain findings in head trauma patients of different age groups.

Methodology: This was a cross-sectional descriptive epidemiological study. It included 45 head injury patients who presented to the Emergency Department of Sharif Medical City Hospital, Lahore, Pakistan and underwent a CT scan. The Glasgow Coma Scale (GCS) score of the patients at the time of presentation to the Emergency Department was calculated and the data was filled in the questionnaire.

Results: Most of the patients were adults i.e they belonged to the age group 19-60 years (68.9%). Out of the 45 patients, 66.7% had a mild, 24.4% had a moderate and only 8.9% had a severe GCS score. The most common CT scan finding in patients with head trauma was a linear fracture (40%) with contusions being the second most common finding (17.8%). Our results showed that 20% of the patients with a severe GCS score had multiple findings on their CT scan reports whereas only 4.5% of the patients with severe GCS had a single CT scan finding. There is a strong association between the GCS score of the patients and the number of findings on their CT bran scan reports. Most of the patients with severe head injury had the subarachnoid hemorrhage.

Conclusion: This study showed that there is a strong relationship between the GCS score of the patients with head injury and the likelihood of multiple findings on their CT scan reports.

Keywords: *Glasgow Coma Scale (GCS). CT Scan Brain. Head Trauma.*

INTRODUCTION

Head injury is a common and potentially devastating clinical problem. Within 48 hours of head injury, clinical intervention should be done for the proper management of head trauma. For the patients with head injury, computed tomography (CT) scan of the brain can perform an important role in the diagnostic workup. In the initial stages, neuroimaging is very significant to find out the existence and the extent of the injury and determine the surgery or minimally invasive interventions. Computed tomography (CT) scan is the best imaging modality to be performed in head injury patients in emergency and trauma setup due to its easy availability, low cost and less time required to perform it. The use of CT scan brain in head injury patients has become increasingly common. Because of separate CT scan windows for brain and bone, it not only gives details of intracranial pathologies but also gives excellent clue about cranial, skull base and facial bones fractures.[1] Glasgow Coma Scale (GCS) is a quantitative measure of the conscious level of the patient. It is the best assessment tool for the patients with head injury.

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Glasgow Coma Scale was first presented by Teasdale and Jennett in 1974 and is scored from 3-15 (15 being the fully conscious patient and 3 being the one showing no response to pain.[2] According to GCS, head injury patients can be divided into three groups; mild, moderate and severe. Patients with mild head injury have GCS between 13-15, moderate have GCS between 9-12 and in severe head injury GCS is 3-8. Glasgow Coma Scale is shown in table 1. Head injury is a common problem seen in poly-trauma patients.[3,4] It is an alarming health problem worldwide with an increasingly high incidence and suggesting a dominant and prime cause of death and disability in all age groups i.e. adolescent, adult and geriatric. It is also a major cause of morbidity and mortality in Pakistan.[5] Radiological evaluation of head injury patients includes an x-ray of the skull and CT scan brain. Selection of patients for CT scan is done on the basis of Glasgow Coma Scale, signs of raised intracranial pressure and presence of skull fracture.[6-10] Head injury is very common in Pakistan. So, this study was planned to evaluate the relationship between GCS score and CT scan brain findings in head trauma patients of different age groups.

METHODOLOGY

This was a cross-sectional descriptive epidemiological study. It included head injury patients who presented to

the Emergency Department of Sharif Medical City Hospital, Lahore, and underwent a CT scan. A non-probability sampling technique was used. Forty five patients were included in this study. It was carried out between September 2016 - January 2017 after approval from ethical committee. Written informed consent was taken from the patients and data was collected using a questionnaire. The Glasgow Coma Scale (GCS) score of the patients at the time of presentation to the Emergency Department was calculated and the score together with the findings of their CT scan reports was filled in the questionnaire. Study subjects were divided into three groups according to age. Group 1 with the age <18 years, group 2 has patients of age 19-16 years and group 3 included patients with age > 60 years.

This division is based upon the premise that the mechanisms of injury in group 1 (play related falls, over speeding, one-wheeling) are generally significantly different from those in group 2 (accidental trauma, work-related injuries). The second division is based upon both the different mechanisms as well as the existence of co-morbidities in patients of group 3 (brain atrophy, atherosclerosis).

STATISTICAL ANALYSIS

The data collected through the questionnaires was entered into the computer using the SPSS (Statistical Package for Social Sciences) software 23.0. The categorical variables were analyzed and presented as frequencies and percentages. Their association with the patient GCS score was analyzed using chi-square test. A p-value of < 0.05 was considered statistically significant.

RESULTS

Most of the patients belonged to the age group 19-60 years (68.9%), 71.1% of the patients were male whereas only 28.9% of the patients were females (Figure 1).

Our results showed that most of the patients (68.9%) suffered from the head injury due to a fall from height and 14 (31.1%) patients presented after road traffic accident. Out of the 45 patients, 66.7% had a mild, 24.4% had a moderate and only 8.9% had a severe GCS score. The most common CT scan finding in patients with head trauma was a linear fracture (40%) with contusions being the second most common finding (17.8%). There was an equal incident of subdural hematoma (SDH) and extradural hematoma (EDH) in the patients (11.1%) with a slightly higher incidence of subarachnoid hemorrhage (SAH) (15.6%) (Table 2).

Our results depicts that 58.3% of the patients in the age

Table:1 Glasgow Coma Scale

Parameter	Response	Score
Eye-opening	Spontaneous	4
	To command	3
	To pain	2
	No response	1
Motor response	Obeys	6
	Localizes	5
	Withdrawal	4
	Flexor	3
	Extensor	2
	No response	1
Verbal response	Oriented	5
	Confused conversation	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No response	1

Table 2: Frequency distribution of patients according to their CT scan findings

CT Scan Findings	Percentage
Linear Fractures	40
Partially Displaced Fractures	4.4
Depressed Fractures	2.2
Comminuted Fractures	0
Midline Shift	2.2
Contusions	17.8
Diffuse Cerebral Edema	6.7
Soft Tissue Swelling	11.1
Intracranial Hemorrhage (ICH)	0
Pneumocephalus	2.2
Subdural Hematoma (SDH)	11.1
Subarachnoid Hemorrhage (SAH)	15.6
Extradural Hematoma (EDH)	11.1
Incidental Findings	2.2
Unremarkable scan	15.6

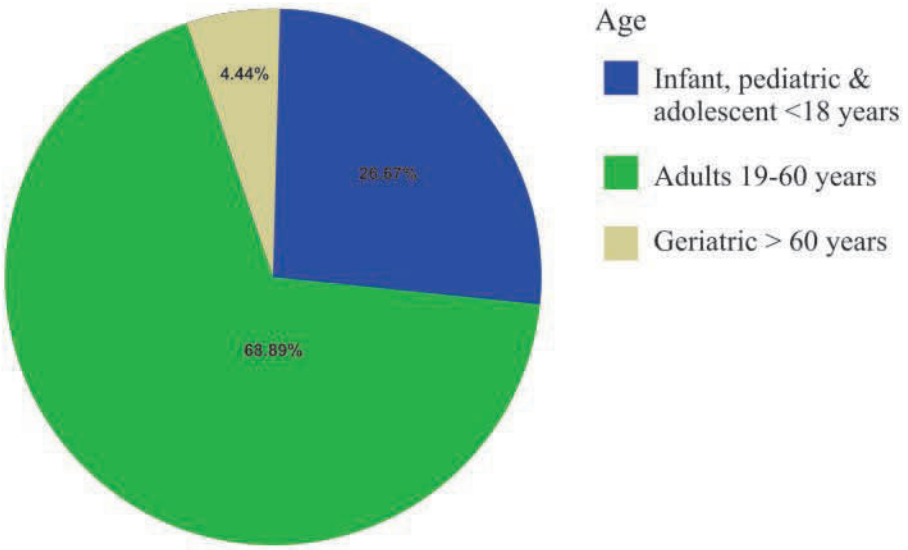

Figure 1: Age distribution of the patients

group <18 years and 67.7% of the patients in the age group 19-60 years had a mild head injury. However, there is no statistical significance between the patients GCS scores and their age ($p > 0.05$).

In our study, 20% of the patients with a severe GCS score had multiple findings on their CT scan reports whereas only 4.5% of the patients with severe GCS had a single CT scan finding. There is a strong association between the GCS scores of the patients and the number of findings on their CT scan reports ($p < 0.05$).

Our results showed that 42.9% of the patients with severe head injury had SAH according to their CT scan reports. There is a strong statistical association between the GCS score of head injury patients and the presence of SAH on their CT scan reports ($p < 0.01$ which means results are highly significant).

Table 3: Comparison of the patients GCS score in relation to their age groups

		Glasgow Coma Scale Scores			Total
		Mild (13-15)	Moderate (9-12)	Severe (3-8)	
Age	< 18 years	7	5	0	12
		58.3%	41.7%	0%	100%
	19-60 years	21	6	4	31
		67.7%	19.4%	12.9%	100%
	> 60 years	2	0	0	2
		100%	0%	0%	100%
Total		30	11	4	45
		66.7%	24.4%	8.9%	100%
Chi- square value = 4.544 with p value = 0.337					

Table 4: Comparison of the patients GCS score in relation to the number of findings on their CT scan

		Glasgow Coma Scale Scores			Total
		Mild (13-15)	Moderate (9-12)	Severe (3-8)	
Findings on CT scan	Unremarkable Scan	7	1	0	8
		87.5%	12.5%	0%	100%
	Single finding	18	3	1	22
		81.8%	13.6%	4.5%	100%
	Multiple findings	5	7	3	15
		33.3%	46.7%	20.0%	100%
Total		30	11	4	45
		66.7%	24.4%	8.9%	100%
Chi- square value = 11.588 with p value = 0.021					

Table 5: Comparison of the patients GCS score in relation to the presence of SAH on their CT scan report

		Glasgow Coma Scale Scores			Total
		Mild (13-15)	Moderate (9-12)	Severe (3-8)	
SAH	Present	2	2	3	7
		28.6%	28.6%	42.9%	100%
	Absent	28	9	1	38
		73.7%	23.7%	2.6%	100%
Total		30	11	4	45
		66.7%	24.4%	8.9%	100%
Chi- square value = 12.623 with p value = 0.002					

DISCUSSION

Head trauma is an important public health problem. There are many factors which can affect the severity of head injury and the likelihood of having positive findings on the CT scan, for example, the mechanism of injury (sharp & blunt, acceleration & deceleration factors) and types of injury.[11-13] In this study, 45 post head injury patients in three different age groups the pediatric population, the adult population and the geriatric population were observed. This division was based upon the premise that the mechanisms of injury were different for different age groups. Group 1 have injury due to play related falls, over speeding, one-wheeling whereas in group 2 accidental trauma and work-related injuries are common. In group 3 primarily falls because of age-related co-morbidities usually occur. Another, very valid reason behind this grouping was the age-related differences in the anatomy of the structures involved as well as the existence of co-morbidities. Younger patients have a higher structural compliance with trauma and as the age advances, this ability is lost. Additionally, other factors like brain atrophy and atherosclerosis play a role in the type of injury resulting from similar trauma.

Out of the 45 patients, 68.9% belonged to the age group 19-60 years and 71.1% of the patients were male. In a study by Nayebaghayee et al. similar results showing the majority of the patients in the adult group were observed.[4] This may be because 19-60 years age group forms the majority of the working population in our country and most of them are males so they are more prone to mishaps and accidents.

According to our study, 68.9% of the patients had a traumatic head injury due to a fall from height as compared to the 31.1% who suffered head injury due to a road traffic accident. However, a similar study carried out in Pakistan showed that 62.6% of the injuries were caused by road traffic accidents whereas 31.7% of the injuries were a result of a fall.[5] Both these studies show that RTA and falls are the major causes of head injury in Pakistan. This may be because of poor safety measures and the rash driving practices in Pakistan.

In our study, 66.7% of the patients had a mild head injury, 24.4% had a moderate head injury and 8.9% had a severe head injury according to the GCS score upon presentation in the Emergency Department. Farshchian et al. conducted a study in which 70.13% of the patients had a mild, 7.8% had a moderate and 22% had a severe head injury according to their GCS score.[3]

The most common CT scan finding in our patients with head trauma was linear fractures (40%) with contusions being the second most common finding (17.8%). There was an equal incident of SDH and EDH in the patients (11.1%) with a slightly higher incidence of SAH (15.6%). A similar study carried out in Iran demonstrated that the most common type of lesion on the CT scan was the epidural hematoma (38.5%), followed by cerebral contusion (29.4%) and pneumocephalus (17.4%).[4]

An important point highlighted in this study was that the patients with severe GCS score had multiple findings on their CT scan (20% of patients with a severe GCS had multiple findings). The results were statistically significant with a p-value < 0.05.

A study was conducted by Farshchian et al. to see the correlation between GCS and brain CT scan findings in head trauma patients. According to their study, most of the head trauma patients having low GCS score have 3 positive finding on CT scan showing extra-axial hematoma, subarachnoid hemorrhage and hemorrhage contusion.[3] A study conducted by Lee et al. also revealed the positive association between GCS score and CT scan findings.[1]

However, Nayebaghayee et al. observed opposite results in their study. According to their study, a weak correlation was revealed between the two modalities (CT findings and GCS severity scoring) to determine brain lesions ($p = 0.142$). Two hundred patients were included in this study. Out of 200 patients, 161 patients had GCS 13-15, 21 had GCS 9-12 and 18 had GCS <8. One hundred and nine patients had abnormal brain CT scan findings. Out of these 109 patients, 77.1% had the mild head injury, 11% had moderate head injury and 11.9% had the severe head injury.[4]

CONCLUSION

This study showed that there is a strong relationship between the GCS score of the patients with head injury and the likelihood of multiple findings on their CT scan reports. Patients with severe GCS also had a strong possibility of having subarachnoid hemorrhage (SAH). However, the relatively small number of patients included in this study necessitates further studies for a definitive conclusion to be made.

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Original Article

Lipid Profile in Polycystic Ovarian Syndrome

Salma Haq, Maria Aslam, Zarghoona Jafar

ABSTRACT

Objective: To compare serum lipid profile of the patients with polycystic ovarian syndrome (PCOS) with normal healthy controls.

Methodology: It was a cross-sectional study conducted in the Department of Pathology, Sharif Medical City Hospital, Lahore. The study included 120 subjects between the age of 18- 40 years. They were divided into two groups. Group 1 included 60 patients of PCOS and group II consisted of 60 healthy females of same BMI and age group. Newly diagnosed patients of PCOS based on Rotterdam criteria were included in this study by random sampling technique. Lipid profile was performed on all subjects.

Results: Mean age of the study patients included in group I was 33±7 years and in control group II mean age was 31± 9 years. A statistically significant difference was found when serum lipid profile of both groups was compared. Serum total cholesterol, triglyceride, LDL and VLDL were significantly raised in patients with PCOS while serum HDL was low in the patient group as compared to controls

Conclusion: Total cholesterol, triglycerides, LDL and VLDL levels were high and HDL level was low in patients with PCOS. So, it was concluded that dyslipidemia is an accompanying feature in patients with PCOS.

Keywords: *Polycystic ovarian disease. Dyslipidemia. Insulin resistance. Lipid profile.*

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common causes of endocrine dysfunction in premenopausal women. Its prevalence ranges from 4% to 7% worldwide. Polycystic ovarian syndrome (PCOS) is a reproductive endocrinopathy with multisystem involvement and is characterized by increased adrenal and ovarian androgen secretion and metabolic disturbances. In this disorder patients present with obesity, chronic anovulation, androgen excess and insulin resistance.[1]

It is the most common cause of infertility in females. According to Rotterdam (2003), polycystic ovarian syndrome is defined as having any two of following conditions: 1) Oligo/anovulation, 2) Clinical/ biochemical signs of hyperandrogenism, 3) Polycystic ovaries by scan with the exclusion of other related disorder. The pathophysiology of PCOS involves the hypothalamus-pituitary-ovarian axis, ovarian theca cell hyperplasia, hyperinsulinemia and release of adipocyte-driven factors and other cytokines.[2]

In patients with PCOS binding of insulin to its receptors is inefficient that leads to hyperglycemia and increased insulin secretion from beta cells.[9] Insulin resistance occurs in about 50-80% of patients with PCOS.[4]

Polycystic ovary syndrome has multifactorial etiology with the involvement of genetic, environmental, endocrine and metabolic factors. Patients present with complaints of menstrual irregularity, infertility, hirsutism, acne and various metabolic disorders. Obesity, insulin resistance, dyslipidemia and hypertension are the common metabolic derangements. Women with PCOS can develop cardiometabolic syndrome at an early age.[7] A cardiometabolic syndrome is a group of interlinked risk factors that promote the development of atherosclerosis, coronary artery disease and type 2 diabetes mellitus.[8]

There is a strong influence of obesity on the prevalence of metabolic abnormalities in patients with PCOS. It is associated with a change in lipid and lipoprotein metabolism.[1]

Dyslipidemia is a common metabolic abnormality that occurs in females with polycystic ovary syndrome. Insulin resistance plays an important role in the pathophysiology of dyslipidemia in women with PCOS by stimulation of lipolysis and alteration in expression of hepatic and lipoprotein lipases. Hyperandrogenism in these females leads to increased hepatic lipase. It may also contribute to dyslipidemia and adipocyte dysfunction.[3]

Obesity and insulin resistance can result in increase in long-chain free fatty acids in the portal vein. This causes increased secretion of apolipoprotein B100 by the liver. The long-chain fatty acids affect degradation of apoB in the endoplasmic reticulum. This leads to increased VLDL levels in these patients as compared to the normal and eventually results in hypertriglyceridmia.[4]

In these patients levels of high-density lipoprotein-cholesterol (HDL-C) and apolipoprotein (Apo) A-I are decreased. There is increased secretion of VLDL particle by the liver that results in increased levels of triglycerides (TG), ApoB and very low-density

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lipoprotein.[3-6]
The present study was undertaken to document the lipid abnormalities so that the patients at the risk of cardiometabolic syndrome will be identified.

METHODOLOGY

It was a cross-sectional study conducted in the Department of Pathology, Sharif Medical City Hospital, Lahore. The study included 120 subjects which were divided into two groups. Group 1 included 60 patients of PCOS and group II consisted of 60 healthy females of same BMI and age group. Newly diagnosed patients of PCOS based on Rotterdam criteria were included in this study by random sampling technique. The institutional ethical committee approved the study and informed consent was obtained from all the study subjects.
A proforma which contained details of age, menstrual history, medical history, family history of type 2 diabetes mellitus and polycystic ovarian syndrome was filled by all subjects. Using aseptic techniques, 5 ml of venous blood sample was collected from all study subjects after 12 hours overnight fast. Lipid profile was performed on all samples and results of both groups were compared. Total cholesterol, triglycerides and high density lipoprotein cholesterol were performed on selectra. Total cholesterol was performed by cholesterol oxidase method, triglycerides by glycerol phosphate oxidase and peroxidase method and HDL-C was done by phosphotungstic acid method. LDL-C and VLDL-C were calculated using the Friedewald's formula.

STATISTICAL ANALYSIS

The data was analyzed by using SPSS version 21. Mean & standard deviation was calculated for quantitative variables. Two groups were compared by using t-test.

RESULTS

Mean age of the study patients included in group I was 33±7 years and in control group II mean age was 31±9 years. Mean levels of triglycerides, total cholesterol, HDL and LDL in group I and II were tabulated in table 1. A statistically significant difference was found when serum lipid profile of both groups was compared. Serum total cholesterol, triglyceride, LDL, VLDL were significantly raised in patients with PCOS while serum HDL was low in the patient group as compared to controls (Figure 1).

Table 1: Comparison of serum lipid profile of study subjects

	Cholesterol (mg/dL)	Triglyceride (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	VLDL (mg/dL)
Group I	225.3±15.1	219.6±18.9	28.7±3.08	139.3±4.4	30.5±5.1
Group II	144.4±12.5	126.5±17.2	57.7±72.0	81.9±9.7	22.3±2.1

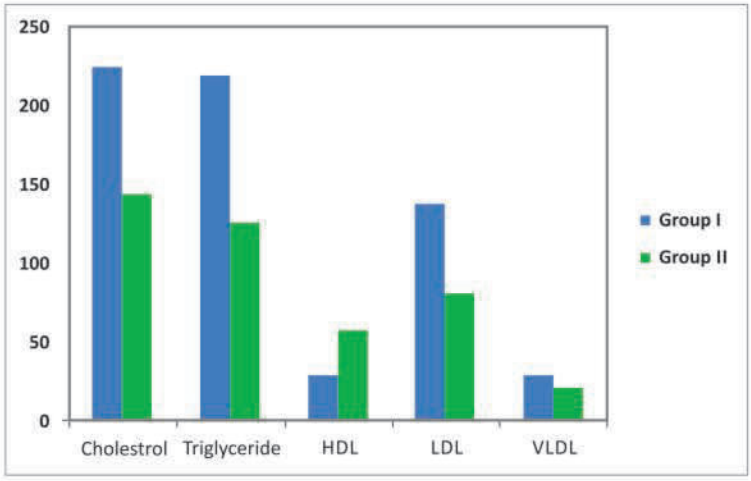

Figure 1: Bar chart showing lipid profile of study subjects

DISCUSSION

Polycystic ovary syndrome is the most frequently occurring endocrine disorder seen in women of reproductive age. It is characterized by menstrual irregularities, insulin resistance and hyper-androgenism.[6]

Dyslipidemia is one of the most perplexing metabolic disturbances that occur in patients with PCOS. Insulin resistance, obesity and hyperandrogenism play a significant pathophysiological role in the development of dyslipidemia in this syndrome.[4]

In this study, we observed a statistically significant difference in the mean levels of total cholesterol, triglyceride, LDL-C and VLDL-C between group I and group II. The mean values of total cholesterol, triglyceride, LDL-C and VLDL-C were higher in patients than controls whereas mean HDL-C values were lower in group I patients as compared to controls. Similar results were found in another study which indicated that levels of triglycerides, cholesterol and LDL-C were increased and HDL-C and apoA-I levels were decreased.[11] A study conducted in Iran showed no significant difference in lipid profile of women with PCOS and healthy controls.[20] This is contrary to our results.

Insulin resistance impairs the ability of insulin to suppress lipolysis. It increases the mobilization of free fatty acids from adipose stores resulting in increased hepatic delivery of free fatty acids. Inhibition of hepatic very low-density lipoprotein synthesis by the insulin is impaired in these patients. All these factors lead to altered catabolism of very low-density lipoprotein.[4]

A study conducted by Cheung et al. compared serum lipid profile in patients with PCOS and controls. They observed that high levels of triglyceride and low HDL were the most common characteristic findings seen in patients with PCOS. These findings were present even in patients with low BMI.[17,18]

Our results are in accordance with the above observations. Elevated triglycerides levels may occur due to resistance to the action of insulin on lipoprotein lipase present in peripheral tissues. The subsequent exchange of triglycerides for cholesteryl ester (CE) by the activity of CE transfer protein (CETP) results in triglycerides enriched high-density lipoprotein (HDL) particles that are catabolized more rapidly and CE-enriched VLDL particles that are converted into small dense low-density lipoprotein (LDL) particles. Insulin resistance may also be responsible for the decreased levels of HDL cholesterol. In spite of increased synthesis of HDL cholesterol, the plasma level of HDL is low due to an increased rate of degradation of apolipoprotein A1/HDL cholesterol. These metabolic derangements might predispose women with PCOS to earlier onset of cardiovascular disease.[4]

Hyperinsulinemia can result from a decrease in insulin clearance as well as from increased insulin secretion. Therefore, in PCOS hyperinsulinemia is probably the result of increased basal insulin secretion and decreased hepatic insulin clearance.[5]

A number of studies showed that the women with PCOS had dyslipidemia in the form of low HDL and high triglycerides.[18,19]

In a study conducted by Sadananjali et al. obese and lean patients with PCOS were compared with control subjects. They also observed decreased levels of HDL cholesterol and high levels of apolipoprotein B, triglycerides and VLDL-C in patients with PCOS. They found no association between lipid profile and BMI.[1]

A study conducted in India showed that in women with PCOS the lipid profile was significantly different as compared to control group. The difference between the mean values of triglycerides ($P<0.001$), total cholesterol ($P = 0.002$) and HDL ($P < 0.001$) was statistically significant two groups but the level of low-density lipoprotein (LDL) ($P <or=0.07$) was not statistically significant.[12]

A study conducted on Korean women with PCOS observed an increased prevalence of dyslipidemia in these patients. Dyslipidemia in PCOS is consistent with the findings that occur in the insulin resistant state i.e decreased levels of ApoA-I and HDL-C and increased levels of triglycerides. Women with PCOS have both qualitative and quantitative changes in LDL-C. Not only LDL-C level is increased in these women but the proportion of atherogenic small dense LDL is also raised.[2]

The present study showed significant atherogenic lipid profile in women with PCOS. This leads to increased risk of cardiovascular disease in these patients. Therefore, increasing awareness of the risk factors, screening of high risk population and early interventions in the form of lifestyle modification and medication will help in prevention of complications of this disease.

CONCLUSION

Total cholesterol, triglycerides, LDL and VLDL levels were high and HDL level was low in patients with PCOS. So, it was concluded that dyslipidemia occurs in patients with PCOS.

It is recommended that lipid profile should be performed regularly in women with PCOS. There is a limitation to this study that in this study effect of BMI on the lipid profile of the patients was not noted.

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Original Article

Patient Referral Trail and Fate of Patients Referred to Surgical and Medical Emergency Department of Services Hospital, Lahore

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ABSTRACT

Objective: To assess the formal referral system and the fate of patients referred to Emergency Department of Services Hospital, Lahore.

Methodology: It was a cross-sectional study conducted in Surgical and Medical Emergency Department of Services Hospital, Lahore. The sample size was estimated by WHO statistical software S size using the formula for estimating a population proportion with specified related precision. At confidence level of 95%, anticipated population proportion of referred patient is 50% and relative precision of 10%. The sample size is 129. A detailed structured questionnaire was used to collect data. The data was analyzed by making tables, estimating their frequencies and percentages.

Results: The study assessed the referral system and fate of 129 patients coming to Surgical and Medical Emergency Department. Out of 129 patients, 10.9% reported to Basic Health Care Units (BHUs), 14.7% reported to Rural Health Care Centers (RHCs), 14.7% reported from District Headquarter (DHQ) Hospital and 59.7% were referred by private clinics or hospitals. Out of these patients, 1.6% were referred by dispensers, 5.4% by lady health workers (LHWs), 24.8% by house officers, 56.6% by medical officers and 11.6% by consultants. Regarding the fate of these patients, 91.5% patients were still admitted, 7.0% were discharged and 1.6% left against medical advice.

Conclusion: Majority of the patients were referred by private sector clinics or hospitals. The main reason for referring a patient is lack of availability of specialist doctors at their available healthcare facility. Health personnel carrying out referrals are not trained to recognize problems that can be treated at their health facility centers. Necessary steps to make patients utilize primary and secondary health facilities need to be put in place, so that only serious patients are screened out for tertiary care facilities.

Keywords: *BHU. RHC. DHQ. Patient referral. Services Hospital, Lahore.*

INTRODUCTION

A referral can be defined as a process in which health care workers at one level of system having insufficient resources like drugs, equipment, skilled healthcare provider to manage clinical condition seek assistance of a better and differently resourced facility at the same or higher level to assist in or take over management of patient case.[1]

The modern referral system was first initiated in the United Kingdom and was well established by 1948 nationalization of hospitals. Patient referral services are an integral part of a well functioning health system. The goal of referral system is to ensure that patient is dealt at an appropriate health facility level and receives cost effective and quality management. In addition, referral also serves to provide linkage between primary, secondary and tertiary care. A referral system at all levels is used as a mean to facilitate flow of patients among healthcare providers.[2]

In many developing countries, the referral is an essential part of preventing unnecessary deaths. In Tanzania, the Ministry of Health encourages referrals from dispensaries and health centers to district hospitals, although no official forms available for those being referred.[2]

The healthcare system in India is plagued by overcrowding, lack of specialist doctors, paramedics and an effective referral system. Pakistan healthcare system is a three tiered healthcare delivery system: primary, secondary and tertiary care. In public health sector, the first rung in referral hierarchy is lady health worker (LHW) of the National program, There are 5000 BHUs, 600 RHCs, 7500 other healthcare facilities and over 100,000 LHWs.[5] There are well-equipped tertiary level teaching hospitals to manage the burden of patients referred from peripheral areas of Lahore.[3]

Tertiary care is specialized consultative health care, usually on referral from primary or secondary medical care personnel and has facilities for special investigations and treatment.[4]

The referring physician has valuable data that can inform healthcare provider, including the history of the current problem, past medical problems, medications, allergies and frequently a concrete assessment and plan for the patient such as hospital admission. This profile supports the creation of a referral system including the nature of the current problem, past medical history and medications upon arrival of the patient in the hospital. The patient is identified as the referral and the transfer

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document should be incorporated into the concerned department. If the patients are treated at the first level referral center they may be referred back to the original primary healthcare center with the necessary follow-up advice. This will enhance the trust towards the primary care centers by the patients from the catchments areas.[5] The study aims at evaluating the barriers and constraints to the referral system in our healthcare system at different levels and appraise the access to healthcare system provider and interaction between primary, secondary and tertiary healthcare centers. This will also help in determining the best disciplines to provide comprehensive and integrated healthcare to patients.

METHODOLOGY

It was a cross-sectional study conducted in Surgical and Medical Emergency Department of Services Hospital, Lahore. This is a tertiary care hospital having 1196 Beds comprising of 31 departments. One twenty nine patients referred to emergency department of services hospital were included in this study using non-probability convenient sampling. A data collection tool was objectively developed and pre-tested in the Surgical and Medical Emergency Department. A data collection team consisting of 4th year medical students was organized and trained for the data collection. A detailed structured questionnaire was used to collect data. Face to face interview was conducted. The questionnaire was translated into local languages i.e. Urdu & Punjabi. Both open and close ended questions with multiple options were used. Permission from hospital review committee was taken. All the respondents were explained the purpose of study and informed consent was taken from them.

STATISTICAL ANALYSIS

SPSS version 21.0 was used for data entry and analysis. For qualitative variables, frequency and percentage distribution tables are granted. For inferential statistics, the chi-square test was used.

RESULTS

The study shows that out of 129 patients, 77(59.7%) had the previous history of medical or surgical illness while 52(40.3%) came for the very first time. Fourteen (10.9%) reported to BHU, 19(14.7%) reported to RHC, 19(14.7%) visited DHQ and 77(59.75%) went to private clinics or hospitals respectively.

Our results showed that 59(45.7%) patients were referred because of no specialist was available, 11 (8.5%) were referred due to non-availability of medicines, 25(19.4%) were referred because of no equipment and 34(26.4%) were referred due to any other reasons, mainly due to no improvement in their health.

Regarding the healthcare providers, 2(1.6%) patients were referred by the dispensers, 7(5.4%) were referred by LHWs, 32(24.8%) were referred by house officers, 73(56.6%) were referred by the medical officers and 15 (11.6%) were referred by the consultants. After referral decision, 38(29.5%) were provided by discharge slip, 30(23.3%) were given a referral letter and 61(47.3%) were referred verbally. It was noted that in Services hospital, 22(17.1%) were attended by house officers, 52 (40.35%) by the medical officers, 42(32.6%) by postgraduate trainees (PGRs), 11(8.5%) by the registrars and 02(1.6%) by the consultant. It shows that majority of the patients had their first interaction with medical officers. Fifty five (42.6%) were advised laboratory tests and 74(57.4%) were asked for radiological tests i.e. ultrasound and x-rays etc.

Sixteen (12.4%) patients were not satisfied with basic facilities provided while 113(87.6%) said they were well diagnosed and treated after referred from their first contact.

The fate of 10 (7.8%) patients were decided by house officers, 63(48.8%) by the medical officers, 33(25.6%) by the consultants, 15(11.6%) by assistant professors and 8(6.2%) by professors. It shows that fate of most of the cases was decided by medical officers.

Table 1: Healthcare facilities from which patients are referred to Services Hospital

Healthcare Center	Number of Patients Referred	
	Frequency	Percentage
BHU	14	10.9%
RHC	19	14.7%
DHQ	19	14.7%
Private	77	59.7%

Table 2: Reasons for referral of patients to Emergency Department of Services Hospital, Lahore

Reasons for referral of patients	Frequency	Percentage
Specialist not available	59	45.7%
Medicine not available	11	8.5%
Equipment not available	25	19.4%
Any other reason	34	26.4%

Table 3: Mode of documentation used by previous facility for referral

Mode of Documentation	Frequency	Percentage
Discharge slip	38	29.5%
Referral letter	30	23.3%
Verbal	61	47.2%
Total	129	100%

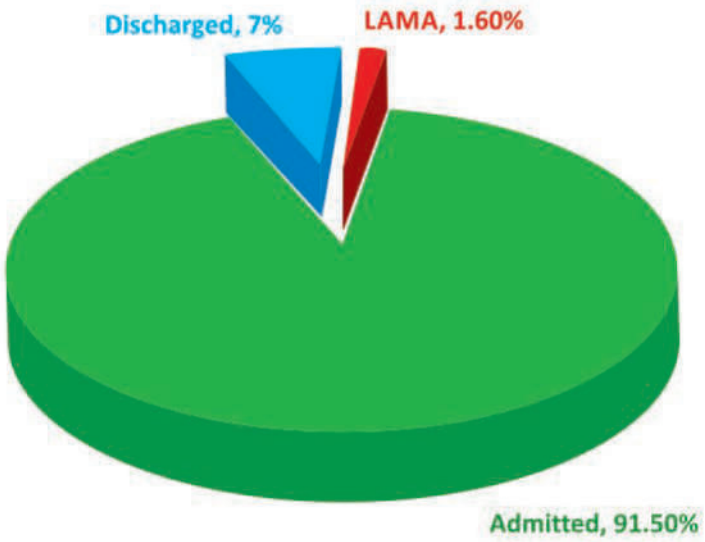

Figure 1: Fate of Referred Patients

DISCUSSION

A two-way referral system is advocated from the lowest level of health care to highest except in emergency when patients can be referred to any of the facilities for immediate treatment. This is hardly the case in many of the developing countries. The current study attempts to point out deficiencies in the referral system of the public sector. One hundred and twenty nine patients who were interviewed went through the referral system.

It is obvious from above analysis that majority of patients (59.7%) are being referred by the private sector. In Pakistan, private medical care is omnipresent in both urban and semiurban areas and extends also to rural areas. It enjoys a great popularity amongst our patients and is utilized more than public services. However, it is the primary role of health services to strengthen public sector and make it more reputable. These results are in accordance with Akande who carried a study in a tertiary care hospital in Nigeria about the referral system of patients. Although there is a well defined three level system of health facilities for the patient but according to the survey, it was pointed that most of patients directly attend the tertiary care

units on their own without any prior visit to primary or secondary units. Furthermore, the private practitioners also refer patients to the tertiary health care without referral to basic setups. All these breaches in the regular referral system leads to compromise on the effectiveness of the system by creating overload on tertiary units.[6]

This study also implores that patients were not diagnosed properly at previous healthcare centers or they were not satisfied with the therapeutic interventions. Omaha et al. conducted a study on patient referral system in the Republic of Honduras. They narrated that referral in health system is the backbone of the patient treatment chain. Thus there is need to develop confidence in family practitioner and physicians who are the first point of call on getting to tertiary center and there is need to organize medical education for family physician in treatment of simple disease. The need for early referral shows that family physician has doubt in diagnosis.[28] These results are in line with our study and we should make proper arrangements to improve this situation.

In our study, only 5.4 % patients were referred by LHWs while 56.6 % were referred by medical officers. This is in accordance with another study conducted by Mumtaz et al. According to him, there is a marked observed barrier in area wise gender discrimination, therefore in some areas, only the lady health workers can guide and educate the population of the same gender.[8]

Out of 129 patients, 94.6% respondents thought that referral was necessary while 5.4% were not in favor of this decision. This is in contrast to another study which showed that in the general referral system of developed countries only a very small percentage of patients attending the primary health unit need to be referred to secondary or tertiary units except those in the emergency or severe ailment.[7]

This study also illustrates that main cause of referral is non-availability of the specialist doctors at primary and secondary healthcare facilities. Patients often used to visit their nearby private clinics where emergency facilities and professional staff is absent so they immediately refer patients to tertiary care hospitals verbally (47.3%) and very few provide discharge slips (29.5%). This is in accordance with a study conducted by Roland et al. He found that the referral rates vary depending upon availability of physician consultants, prescribing rates were analyzed for thoracic medicine, psychiatry, dermatology and medicine. Results came out to be referrals proportional to availability of consultants while roughly related to need for outpatient services. Referral rates were influenced greatly by availability of the consultants.[9]

These results are contrary to a study conducted in the USA which concluded that due to the clinical confusion there is stress and difficulty in physician's decision making ability. Younger physicians had higher referral rates. Stress from uncertainty, heavy workload and loss of control over practice environment were associated with heavy referrals.[7]

CONCLUSION

Majority of the patients were referred by private sector clinics or hospitals. The main reason for referring a patient is lack of availability of specialist doctors at their available healthcare facility. Health personnel carrying out referrals are not trained to recognize problems that can be treated at their health facility centers. Although most of the people were not satisfied with the quality of treatment provided and behavior of staff still they were admitted. Necessary steps to make patients utilize primary and secondary health facilities need to be put in place, so that only serious patients are screened out for tertiary care facilities. Instead of referring a patient verbally, proper documentation must be provided that must include the admission date, diagnostic details, treatment provided and the investigations carried out along with the reason of transferring the patient. Appropriate communication with respect to referral must be made with the relatives and the receiving unit or health facility.

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Original Article

Pattern of sFlt-1 Antiangiogenic Serum Marker in Pregnancy-Induced Hypertension in Sharif Medical City Hospital, Lahore

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ABSTRACT

Objective: To investigate the maternal serum level of antiangiogenic factor sFlt-1 in pregnancy-induced hypertension (PIH) at different gestational ages in Sharif Medical City Hospital (SMCH), Lahore.

Methodology: The present descriptive case-control study evaluated maternal serum levels of antiangiogenic marker sFlt-1 in 90 women with gestational age 18-40 weeks referred to SMCH, Lahore. It included 69 pregnant women with hypertension and 21 normotensive pregnant control subjects. The hypertensive patients were taking methyldopa. Out of 69 hypertensive pregnant subjects, 24 had gestational hypertension (GH), 41 had preeclampsia (PE) and 4 had eclampsia (EC). The indicators of blood pressure, urinary albumin and convulsions were the principals in categorizing the hypertensive pregnancy in GH, PE and EC. The age, parity, BMI, urinary albumin and hemoglobin were also noted and measured. The antiangiogenic serum biomarker was analyzed and assessed with enzyme-linked immunosorbent assay (ELISA).

Results: The average serum concentration of sFlt-1 was 33% lower in hypertensive pregnant women as compared to normotensive control subjects. The difference was statistically significant (p=0.05). In GH, sFlt-1 concentration was 28% lower than controls. In PE, sFlt-1 level was 37% lower than the normotensive subjects and in EC patients, sFlt-1 level was 25% lower than the normotensive subjects. It had been observed that PE subjects exhibited a maximum decrease in sFlt-1 among all hypertensive subjects. There is also a significant difference in sFlt-1 levels at different gestational ages.

Conclusion: The serum sFlt-1 levels in pregnancy-induced hypertension women are higher than normotensive women. In our study, the serum levels of antiangiogenic factor sFlt-1 in pregnancy-induced hypertension are lower than normotensive pregnant women. This is attributed to the use of methyldopa in these patients.

Keywords: *Antiangiogenic marker sFlt-1. Pregnancy-induced hypertension. Preeclampsia. Eclampsia.*

INTRODUCTION

Hypertension in pregnancy is common worldwide and accounts for 12% maternal mortality during pregnancy and puerperium.[1] Hypertensive disorders in pregnancy (HDP) cause severe maternal obstetric complications, preterm delivery, fetal intrauterine growth restriction, low birth weight and perinatal death. The different categories of HDP are gestational hypertension, preeclampsia and eclampsia.

The probable causes of pregnancy induced hypertension are abnormal placentation, vasculopathy, inflammatory changes, immunological factors, genetic factors and nutritional factors.[2] The incidence of PIH varies with age, parity, geographic distribution and socioeconomic status. The risk factors for pregnancy-induced hypertension are age under 20 and over 35 years, first pregnancy, previous history of severe PIH, family history of preeclampsia, short stature, migraine, chronic renal disease and diabetes mellitus.[3]

Although the etiology remains unidentified, placental hypoperfusion and diffuse endothelial cell injury are considered to be the central pathologic events. Reduced perfusion as a consequence of abnormal placentation is supposed to lead to ischemia-reperfusion damage to the placenta.[4] In pregnancy-induced hypertension, there is an insufficient maternal vascular response to placentation leading to ischemic changes. Various noxious substances are released from the placenta and deciduas. These serve as mediators to provoke endothelial injury.[4,5]

Recent data demonstrates that antiangiogenic proteins including soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng) and proangiogenic protein placental growth factor (PLGF) are expressed in large amounts various weeks prior the onset of clinical indications and symptoms of PIH.[5] An imbalance of placental-derived antiangiogenic factors may play a main role in facilitating endothelial dysfunction. Alternative splicing of Flt-1 results in the formation of sFlt-1. This cannot fasten to cell membranes and is secreted into the maternal bloodstream leading to high serum levels. It can antagonize vascular endothelial growth factor (VEGF) and placental growth factor by binding to them and avoiding their interface with endogenous receptors.[5]

Khalil et al. suggested that alpha methyldopa may have

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a precise effect on placental and/or endothelial cell function in preeclampsia mothers, changing angiogenic and antiangiogenic proteins. Methyldopa has been correlated with a noteworthy reduction in maternal serum of sFlt-1.[6,12,13]

The incidence of pregnancy-induced hypertension is comparatively higher in Pakistan. Thus to understand the pathogenesis, sFlt-1 is assessed in different categories of HDP to understand its association with the disease. It may assist in prediction and diagnosis of pregnancy-induced hypertension.

METHODOLOGY

This case-control descriptive study was performed over the period of six months. Written informed consent was obtained from all patients participating in the study and they were assured about the privacy of data. The study was approved by ethics committee of the institution.

Ninety pregnant women with gestational age between 16 weeks to term (38 weeks), referred to SMCH were enrolled in the study. Sixty nine women were hypertensive and 21 were normotensive. The hypertensive patients were taking methyldopa. After obtaining informed consent, 3 ml blood sample was taken using aseptic measures. The relevant history was filled in questionnaires including age, obstetric history, smoking habits, headache, blurred vision and medication intake. Gestational age was based on last menstrual period and first trimester or early second-trimester ultrasound.

Pregnant women with the blood pressure more than 140/90 mmHg in the twentieth week of gestation on two occasions at least six hours apart were labeled as hypertensive. The hypertensive patients without proteinuria were included in the category of gestational hypertension (GH), with proteinuria more than 300mg/24 hrs or 1+ protein on the dipstick with midstream urine sample were categorized in preeclampsia, convulsions with or without proteinuria were grouped as eclampsia. The inclusion criteria for all groups were age 18 and 40 years, singleton pregnancy, non-molar gestation, nonsmoker and no history of hypertension before pregnancy. The exclusion criteria were patients with the history of chronic hypertension, renal diseases, liver disease, cardiovascular disease, diabetes and other problems that may threat mother or fetus. Out of 69 hypertensive pregnant women, 24 had gestational hypertension, 41 had preeclampsia and 4 had eclampsia. The serum level of sFlt-1 was determined by ELISA kit.

STATISTICAL ANALYSIS

In the comparison of various groups, the mean & standard error of mean was calculated and the significance of difference between groups and subgroups was determined with an independent t-test. The data were analyzed using SPSS version 21.0. The significance of difference was taken at $p < 0.05$.

RESULTS

The average age in normotensive and hypertensive pregnant subjects was 18-30 years. Sixty nine hypertensive and 21 normotensive pregnant women were included. In this study, most of the hypertensive pregnant women were of younger age. Preeclampsia affected subjects had increased body mass index (BMI). Hypertension was common in multiparous subjects compared to nulliparous women. Out of 69 hypertensive patients, 24 patients were categorized in gestational hypertension, 41 in preeclampsia and 4 in eclampsia.

The average concentration of sFlt-1 in normotensive control pregnant subjects was 3956±681ng/L. The mean value of sFlt-1 in hypertensive subjects was found 2619±234.5ng/L. In hypertensive subjects, sFlt-1 level was 33% lower than normal subjects and the difference was statically significant (p=0.05). There had been noticeable differences in sFlt-1 levels in different categories of hypertensive subjects. In GH, sFlt-1 concentration was 2825±395ng/L which was found to be 28% lower than controls. In PE, sFlt-1 level was 37% lower than the normotensive subjects and in EC patients, sFlt-1 level was 25% lower than the normotensive subjects. It had been observed that PE subjects exhibited maximum decrease in sFlt-1 among all hypertensive subjects. In PIH and EC, the difference was not significant (Table 2 and Fig. 1).

During 18-28 weeks of pregnancy, there was 19% increase in the marker concentration in GH whereas it exhibited lower concentration in other categories of hypertension compared to the controls. There was however no significant difference among all hypertensive groups during 18-28 weeks of gestation in comparison to normotensive group.

Table 1: Distribution of the study subjects in different categories of hypertension

Distribution	Total	Normotensive	Hypertensive	GH	PE	EC
No. of Subjects	90	21	69	24	41	4
Percentage	100	23.33	76.67	26.67	45.5	4.5

Table 2: sFlt-1ng/L in the study subjects

Groups	Number	Mean±SEM	Difference of hypertensive patients to controls (%)	p-value
Normotensive	21	3956±681.0		
Hypertensive	69	2618±234.5	33% lower	0.05
GH	24	2824±395.3	28% lower	0.160
PE	41	2466±312.5	37% lower	0.005
EC	4	2944.87±88.65	25% lower	0.540

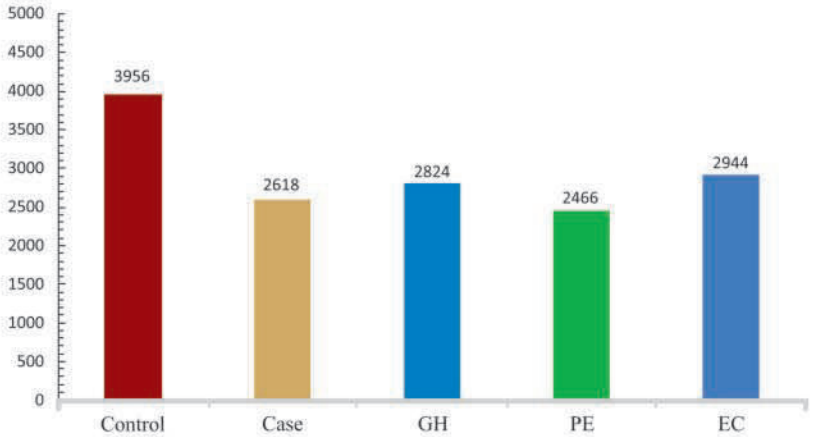

Figure 1: Comparison of sFlt-1ng/L in the study subjects

During 29-35 weeks of gestation, the marker concentration was lower in all hypertensive cases except EC. The PE group was the only one which was statistically significant (p = 0.068).There was 37% decrease in the marker concentration in PE whereas it exhibited 8% higher concentration in EC group compared to the controls. There was however no significant difference in PIH during this phase of gestation in comparison to normotensive (control) group. During 36-40 weeks of gestation, sFlt-1 levels are decreased in all hypertensive patients but it is non-significant statistically.

DISCUSSION

In normotensive pregnancy, antiangiogenic factor soluble fms like tyrosine kinase receptor 1(sFlt-1) level is constant during the first and middle trimester of gestation and there is a marked increase beginning at 33-36 weeks. According to different studies, there is a marked variation in serum marker levels within the same gestational age. It may be due to the difference in sample handling, processing and laboratory procedures. There is no definitive cut-off value to predict pregnancy induced hypertension.[14] So far numerous studies provided the association between the alteration of angiogenic and antiangiogenic factors and subsequent development of pregnancy induced hypertension.[7] Similar findings were reported in other studies.[8,9]

In our study, sFlt-1 level was 33% lower than the normotensive pregnant normal subjects and the difference was statically significant (p=0.05). Additionally, there had been noticeable differences in sFlt-1 levels in different categories of hypertensive subjects. In GH, sFlt-1 concentration was found to be 28% lower than controls. In PE, sFlt-1 concentration was 37% lower and in EC, it was 25% lower than the pregnant normotensive subjects. It had been observed that PE subjects exhibited the lowest decrease in sFlt-1(37%) among all the hypertensive subjects. In PIH and EC, the difference was not significant. (p=0.16, p=0.54).

In our study, the analysis of this factor concentrations in different phases of pregnancy had been performed; the phases were 18-28, 29-35 and 36-40 weeks of the pregnancies. The concentrations of sFlt-1 were markedly greater in GH and comparatively lower in PE and EC collectively from the normotensive pregnancies at 18-28 weeks. The level of the factor was lowered at 29-35 weeks of pregnancies in GH and PE than the normotensive subjects. There was 8% increase in sFlt-1 in EC group. At 36-40 weeks, sFlt-1 levels are decreased in all hypertensive patients but it is non-significant statistically. The pattern is certainly revealing a relationship between the factors and the phases of pregnancies in our sample population.

In PIH cases, there is amplified antiangiogenic property thus causing inconsistent angiogenesis. A patterned appearance of the angiogenesis-related factors is the requirement during pregnancy and changes in the pattern is the reason or result of the vascular disorder.[8,10,11] The hypertensive study subjects were taking methyldopa. There are a few reports regarding the influence of methyldopa on the angiogenesis related humoral factors. Khalil et al. showed that antihypertensive drugs like methyldopa may have a definite role in placental and endothelial cell function in pregnancy-associated hypertension patients, leading to decreased antiangiogenic sFlt-1 in preeclampsia but not in gestational hypertension.[6]

In our study, it has been observed that administration of methyldopa (Aldomet) significantly decreased the level of serum sFlt-1 levels with a positive effect on the control of the disease. The present study, however, observed there was reduced serum level of sFlt-1 at different gestational ages of hypertensive pregnant women as compared to normotensive control pregnant women at the same gestational ages. This contrast could be due to discrepancies in the study population (for example age, parity, BMI, ethnicity, smoking position, genetics) or on the definite onset of HDP versus the diagnosis of HDP.

CONCLUSION

The serum sFlt-1 levels in PIH women are higher than normotensive women. In our study, the serum levels of antiangiogenic factor sFlt-1 in pregnancy-induced hypertension are lower than normotensive pregnant women. This is attributed to the use of methyldopa in these patients.

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Original Article

Association of Obesity and Knee Osteoarthritis

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ABSTRACT

Objective: To determine the association between obesity and severity of knee osteoarthritis.

Methodology: It was a cross-sectional descriptive study conducted in the Department of Orthopaedics Surgery, Sharif Medical City Hospital, Lahore. Study duration was twelve weeks. Fifty (50) patients fulfilling the inclusion criteria were included in this study. Non-probability, purposive sampling technique was used. Anthropometric assessment was performed and radiographs in orthogonal views were taken. Body mass index (BMI) was calculated and knee osteoarthritis grading according to Kellgren and Lawrence (K & L) was done on radiographs. The clinical complaints, radiological assessment and BMI were compared.

Results: Out of 50 patients, 29 were females (58%). Seven (14%) patients presented with mild OA knee, 19 (38%) with moderate OA and 24 (48%) had severe OA. There was a strong correlation between increased body mass index (BMI > 30 kg/m^2) with the severity of OA knee. Moreover, BMI tends to increase with age as well.

Conclusion: Obesity has a strong association with knee osteoarthritis. Obesity increases the incidence and progression of knee osteoarthritis.

Keywords: *Osteoarthritis knee. Body mass index. Obesity.*

INTRODUCTION

Obesity is very common worldwide. According to World Health Organization (WHO), the prevalence of obesity in South East Asia is on a rise and approximately 7 % of adult population has a BMI more than 30 kg/m^2. Although both genders are involved but female gender is relatively at a higher risk.[1] The incidence has become twice globally in the past 30 years. About half a billion people in the world are obese. The obesity is prevalent in both developed as well as developing countries.[2] It is associated with increased morbidity and mortality.[3] Both genetic and environmental factors play a role in causing obesity.[4] Obesity is a risk factor for chronic diseases such as hypertension, dyslipidemia, type 2 diabetes, cardiovascular disease, sleep apnoea, musculoskeletal disorders and some cancers. The risk of death from all causes increases due to obesity in both males and females of all age groups.[5] The obesity causes degenerative and inflammatory diseases of the musculoskeletal system, with the greatest burden resulting from osteoarthritis (OA).[6]

Osteoarthritis (OA) of the knee is the most significant musculoskeletal condition associated with obesity. It is signified by joint pain, stiffness and impaired movement. It is caused by thinning of joint cartilage, which results in reduced joint space and rubbing of bone together. This results in localized inflammatory reaction and eventually stiffness in the surrounding tissue.[7] Currently, 10% population is suffering from OA and its prevalence increases with age.[8] Obesity has a strong relationship with OA and is considered as the greatest modifiable risk factor.[9] Coggon et al. reported that subjects with a BMI>30 kg/m^2 were 6.8 times more likely to develop knee OA than normal-weight controls.[10] Osteoarthritis affects all aspects of life through pain and limitation of mobility. It was estimated that the economic burden of OA in the USA was second only to diabetes in obesity-associated conditions.[11] The burden of this disease is expected to increase, due to the prevalence of obesity and increased longevity. The rationale of this study was to determine the association of knee osteoarthritis with obesity. So that weight reduction and lifestyle modification can lead to decrease mortality and morbidity related to the disease.

METHODOLOGY

It was a cross-sectional descriptive study carried out in the outdoor patient department (OPD) of Orthopaedics Surgery Department, Sharif Medical City Hospital, Lahore. Fifty patients of both genders and age between 25-65 years with primary osteoarthritis of one or both knees were included in the study. Probability sampling technique was used.

Patients with the history of trauma to knees, infection of bone or joint (clinical and radiological), pathological fracture (clinical and radiological) and previous history of any procedure performed on the knee were excluded. The study was approval from the ethical committee of the hospital. Informed consent was taken and history proforma was filled. Anthropometric assessment was performed and radiographs in orthogonal views were taken. Body mass index (BMI) was calculated and knee

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osteoarthritis grading according to Kellgren and Lawrence (K & L) was done on radiographs. The clinical complaints, radiological assessment and BMI were compared.

STATISTICAL ANALYSIS

The collected data was entered and analyzed by SPSS version 23. Descriptive statistics were used to calculate mean and standard deviation for age. Frequency and percentages were calculated. A p-value of <5 was considered statistically significant.

RESULTS

Fifty patients were included in this study. Out of 50 patients, 29 were females (58%) and 21 were males (42%). Mean age of the patients was 48±18 years. Twenty four patients presented with severe OA knee (48%). The grade of OA knee in the patients is shown in figure 1.

Our results showed that there is a strong association between the advancing age and BMI of the patients. In patients of age group 45-65 years, mean BMI was 35 kg/m^2 whereas in patients of age 25- 45 years BMI is comparatively low with mean value 31 kg/m^2.

Out of 50 patients, 7 (14%) presented with mild OA knee, 19 (38%) with moderate OA and 24 (48%) had severe OA. Patients with mild and moderate OA had BMI 28 kg/m$_2$ and 30kg/m^2 respectively whereas BMI of the patients having severe OA was 34 kg/m^2. There is a strong relationship of BMI with the grade of OA knee. The severity of OA knee increased with higher BMI.

DISCUSSION

This study showed that osteoarthritis knee affects female patients more than the male patients. Similar results were also shown in the studies carried out by Hame et al.[11] Another study done by Cho et al. showed similar results.[12]

Our study showed that the BMI of the patients tends to increase with age. The work carried out by Holliday et al. showed similar finding. This occurs due to various factors like lack of exercise, unhealthy eating habits and the slowing of basal metabolic rate.[13]

Our study showed a strong association between BMI and severity of OA knee. The patients with BMI > 30 kg/m^2 presented with severe OA knee. The impact of body mass index (BMI) on incidence and severity of knee was assessed by Jiang et al. They also reported a significant relationship between BMI and risk of OA at both the hip and the knee joint after both clinical and radiological examination. They found a significant association of BMI and knee OA in females as compared to males which was also observed in our study.[14]

In a large population-based cohort study, Reijman et al. investigated the relationship between BMI and incidence and progression of both knee and hip OA. According to them, the mean follow up time was 6.6 years and incidence of knee OA was high in overweight patients. Progression of knee OA was evaluated by decreased joint-space on x-ray and it was found strongly associated with high BMI. No significant relationship was observed between BMI and hip OA.[15]

The severity of structural damage to the joint is directly related to the increased BMI.[22] The multiple factors are involved in the pathogenesis of OA due to obesity. The joint damage occurs due to mechanical factors and metabolic factors. The mechanical factors are decreased muscle strength and increased force on the joints.[16-18]

Obesity is a chronic inflammatory condition that affects multiorgan systems. The metabolic pathways through which obesity leads to joint damage are still unknown. It was supposed that aberrant adipokine expression leads to the destruction and remodeling of joint tissue. Adipokines affect cartilage, synovium and bone. The most abundantly produced adipokines are leptin and adiponectin. Receptors of these adipokines are expressed on the surface of chondrocytes, synoviocytes

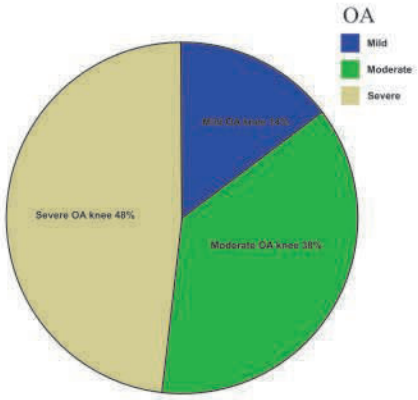

Figure 1: Showing grade of osteoarthritis in patients

and subchondral osteoblasts. Leptin increases the levels of proinflammatory cytokines and various degradative enzymes like nitric oxide and matrix metalloproteinases (MMPs).[19-21] According to a study, leptin and adiponectin levels were significantly high in OA patients as compared to controls.[20]

A study conducted by Richette et al. showed that weight reduction in obese knee OA patients resulted in decreased levels of leptin.[22] Various studies have shown that OA is not just a disease related to aging but also occurs due to metabolic derangement. The metabolic, lipid and humoral mediators contribute to initiation and progression of the disease.[23]

Articular cartilage may not be able to maintain absolute knee adduction movement during walking in obese patients as compared to normal weight individuals. A study done in Japan revealed that obesity related metabolic disorders increased the incidence and progression of knee OA.[25]

CONCLUSION

There is a strong association of increased body mass index (BMI > 30 kg/m^2) with the severity of OA knee. Obesity increases the incidence and progression of knee osteoarthritis. So, weight reduction and lifestyle modification can lead to decreased mortality and morbidity related to the disease.

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Case Report

Decompressive Craniectomy for Malignant Middle Cerebral Artery Infarction with the Postpartum Period and Ebstein Anomaly as risk factors

Farhan Fateh Jang, Muhammad Moosa, Nasir Raza Awan

ABSTRACT

An eighteen years old female presented with sudden onset of left sided weakness two weeks postpartum. Computed tomography (CT) brain revealed right malignant middle cerebral artery (MCA) infarction. The patient underwent decompressive craniectomy (DC) based on the clinical deterioration and imaging studies. This case report discusses DC with or without dural opening as a viable option for the management of pressure caused by malignant MCA infarction the postpartum period and Ebstein anomaly are the risk factors for malignant MCA infarction.

Keywords: *Decompressive craniectomy. Malignant MCA infarction. Postpartum period. Ebstein anomaly.*

INTRODUCTION

Decompressive craniectomy has been performed for many years as a surgical management of the brain tissue compression caused by infarction and other conditions such as cerebral venous thrombosis and traumatic brain injury. However, due to inherent morbidity of primary brain pathology and poor esthetic outcome, the procedure got limited attention.[1] In this case report; we share the experience of DC in a young female patient diagnosed with malignant MCA infarction two weeks postpartum. The postpartum period was considered as the main risk factor for malignant MCA infarction. However, further workup revealed that the patient had Ebstein anomaly, which may have contributed to the malignant MCA infarction.

CASE REPORT

An 18-year-old female patient was admitted in the Department of Neurosciences, Sharif Medical City Hospital, Lahore (Pakistan) with an acute onset of weakness in the left upper and lower extremities. The patient was fully conscious and oriented with Glasgow Coma Scale (GCS) score of 15/15 (Eye_4 + $Motor_6$ + $Verbal_5$) on admission. Pupils were equal in size and reactive to light bilaterally. There was no history of any previously known cardiac disease. CT scan of the brain on admission day showed an ischemic stroke in the right MCA region (Figure 1).

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All laboratory blood tests including complete blood count and coagulation profile were within normal limits. Conservative treatment such as anti-platelets, intravenous fluid and statins was started after obtaining informed consent from the patient's family. Echocardiography performed on second post-admission day suggested atrial septal defect (ASD) and transesophageal echocardiography (TEE) was planned for further evaluation.

The patient started to deteriorate clinically on third post-admission day with left hemiplegia and GCS score of 7/15 (Eye2 + Motor3 + Verbal2) before performing TEE. CT scan of the brain on third post-admission day showed persisting ischemic changes in the right MCA region with cerebral edema and significant mass effect, a condition known as malignant MCA infarction (Figure 2).

The patient underwent immediate DC following clinical deterioration (on 3rd post-admission day), and a large right frontotemporoparietal bone flap was removed temporarily. Written informed consent was obtained from the patient's family before performing surgery. The dura was not opened along with the removal of bone flap as not much pressure of the ischemic brain tissue was observed intra-operatively. The bone flap was placed in the subcutaneous abdominal tissue, and the scalp was closed over the dural membrane. CT scan of the brain on third post-operative day showed decrease in the mass effect (Figure 3), and the patient also improved clinically (GCS score of 12/15).

Two weeks after DC, the patient gained full consciousness with GCS of 15/15. The muscle power in the left upper and lower limbs improved with physiotherapy (from Grade 0 to Grade 2). CT scan of the brain two weeks after surgical decompression showed resolving infarct in the right MCA region with no mass effect (Figure 4).

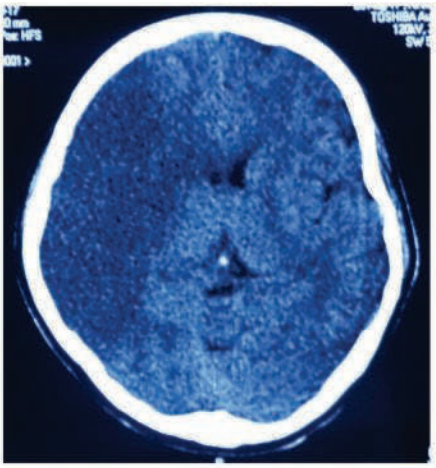

Figure 1: CT scan of the brain showing large hypodense (ischemic) area in the right MCA region with no significant mass effect

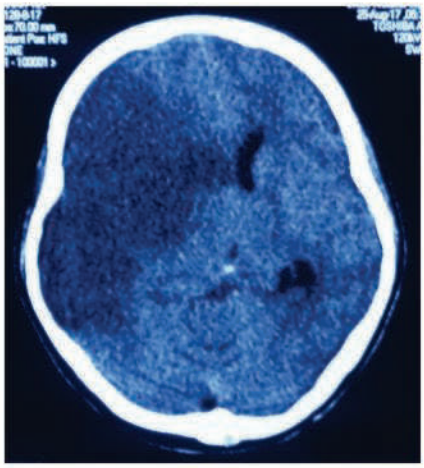

Figure 2: CT scan of the brain on third post-admission day showing hypodense (ischemic) area in the right MCA region with cerebral edema and significant mass effect

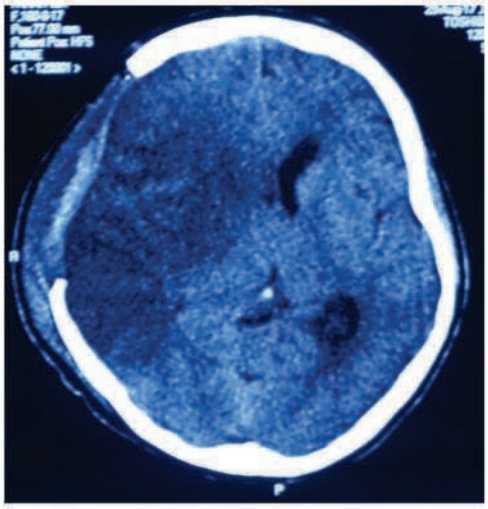

Figure 3: CT scan of the brain on third post-operative day without dural opening showed decrease in the mass effect

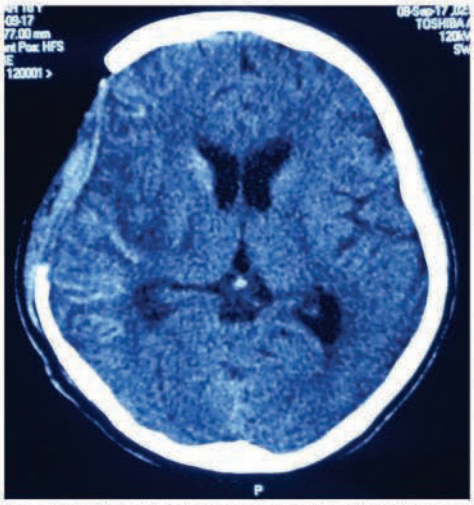

Figure 4: CT of the brain two weeks after DC shows resolving infarct in the right MCA region

Post-operative TEE showed Ebstein anomaly with large ASD. The bone flap was replaced seven weeks after DC, and the patient was referred to cardiac surgeon for the management of Ebstein anomaly.

DISCUSSION

The procedure of lobectomy has been widely replaced by DC as the better surgical option for the management of compression on the brain tissue.[2] The procedure of DC involves temporary removal of a large flap of the skull bone (frontal, temporal, and parietal bones) with or without dural opening to provide space into which the ischemic or injured brain can expand. Decompressive craniectomy can reduce the intracranial pressure (ICP) with the radiological and clinical herniation signs improvement. It can also reduce the spread of the infarcted area and salvage the hypoperfused penumbra.

Malignant MCA infarction is characterized by >50% of MCA distribution area infarction with life-threatening cerebral edema, and the mortality rate of malignant MCA infarction is about 80%.[3] Clinical worsening usually occurs 24-72 hours after the onset of ischemic lesion. Once the patient starts to deteriorate clinically, the role of conventional therapies including osmotherapy, hypothermia, and mechanical ventilation to decrease the ICP becomes limited.[4] In this case, the patient started to deteriorate on third post-admission day. Therefore, we performed immediate DC.

Various methods of DC such as, frontotemporoparietal, sub-temporal, circular and bifrontal decompression methods have been applied to lower the ICP after malignant MCA infarction or traumatic brain injury.[5-8] Frontotemporoparietal DC is a more widely used

method and it has been demonstrated that this method can provide as much as additional space of 92.6 cm^3.[6] Therefore, we performed frontotemporoparietal DC in this case to gain maximum space for decompression.

Dural opening is usually performed combined with DC in order to gain maximum brain expansion. However, not much data is available to compare the outcome of DC with and without dural opening, especially in malignant MCA infarction. In this case, we did not open the dura along with the removal of bone flap as not much pressure of the ischemic brain tissue was observed intra-operatively.

The postpartum period has been identified as the greatest risk for ischemic stroke.[9,10] This may be because the puerperium is a pro-thrombotic state.[11] Our patient had two weeks post-partum history. So, our immediate impression of the main risk factor causing malignant MCA infarction, in this case, was the postpartum period.

However, TEE showed Ebstein anomaly. Ebstein anomaly is a rare congenital heart defect accounting for <1% of all congenital heart diseases, and mainly affects the tricuspid valve. It has been reported that paradoxical embolism due to the atrial septal defect (right to left shunt) can cause cerebral ischemic insult in young patient with Ebstein anomaly.[12] Therefore, Ebstein anomaly may also be the risk factor for malignant MCA infarction in this case.

We concluded that the postpartum period and Ebstein anomaly can be risk factors for malignant MCA infarction in young patients, and DC with or without dural opening can be used as neurosurgical option for treating clinically deteriorating patients with malignant MCA infarction.

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Content Index

JSMDC-Vol. 03, Issue 02

EDITORIAL

ORIGINAL ARTICLES

Content Index

JSMDC-Vol. 03, Issue 02

Author Index

JSMDC – Vol. 03

Subject Index

Subject Index

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