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COMPARATIVE ASSESSMENT OF SUBCLINICAL CAROTID ATHEROSCLEROSIS IN HIV PATIENTS AND HEALTHY CONTROLS BY ULTRASONOGRAPHY & ITS CORRELATION WITH ANTIRETROVIRAL THERAPY

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ABSTRACT **Background:** The study was planned to detect an association of HIV infection and sub-clinical atherosclerosis in the form of increased carotid intima-media thickness (IMT)

Methods: 50 HIV patients and 50 matched healthy controls were studied. The HIV patients were further sub classified into those on ART or not on ART. All of them underwent carotid doppler to identify subclinical atherosclerosis in the form of presence of either pathological intima-media thickness (IMT) or atherosclerotic plaque. Mean IMT was calculated in various groups and the statistical analysis done.

Results: The mean IMT in the test group (HIV), ART, Non ART, control groups was 0.746 mm (SD 0.181), 0.817 mm (SD 0.167), 0.58 mm (SD 0.068) ,0.572 mm (SD 0.101) respectively. There is significant difference in the mean IMT of HIV Vs control groups, ART Vs Non ART sub groups. There is no significant difference in mean IMT of Non ART Vs Control group.

Conclusion: HIV patients have higher prevalence of subclinical atherosclerosis and significantly higher mean IMT as compared to Healthy controls. The prevalence of subclinical atherosclerosis is even higher in ART treated HIV patients.

KEYWORDS : HIV / ADS ; atherosclerosis ; carotid intima-media thickness

INTRODUCTION

Human immune virus (HIV) infection and associated Acquired immune deficiency syndrome (AIDS) is a major health challenge. As per the UNAIDS report of 2016 states, 36.7 million worldwide were suffering from HIV infection in the year 2015(1). HIV related morbidity and mortality has greatly reduced after the introduction of highly active antiretroviral therapy (HAART) in the mid- to late 1990s (2,3) .

Cardiovascular diseases (CVD) and atherosclerosis are the number one cause of deaths globally (4) . Sub clinical atherosclerosis is an early stage of atherosclerosis in which there is pathological thickening of arteries in absence of symptoms. Detection of subclinical atherosclerosis has generated lot of interest because the preventive and management strategies at this stage would show maximum benefit to patients. This can be accurately detected non-invasively by doing ultrasonography of carotid vessels as they are easily accessible and represent overall atherosclerotic burden in the vasculature.

Research suggests possible positive association between these two major killer diseases i.e., AIDS and cardiovascular disease due to increased incidence of Myocardial infarction (MI) in HIV patients treated with combination antiretroviral therapy (CART) (5,6). Two possible reasons have been proposed as the underlying cause for this association. The HIV disease itself and or CART used for treating the disease. Jerico C et al. have found that CART is a strong, independent predictor for the development of subclinical atherosclerosis in HIV-infected patients (7). Further studies for example by Maggi et al. showed high prevalence of carotid atherosclerotic lesions on ultrasonography in HIV patients treated with protease inhibitors (a usual component of CART) suggesting possible association between CART and subclinical atherosclerosis (8).

A few studies have been reported from India studying this association between HIV, ART and sub clinical atherosclerosis (9) . A clear understanding of association between them would help in optimizing the treatment strategies and follow up protocols. This pilot project was undertaken to explore these associations in Indian population.

MATERIAL AND METHODS

Inclusion Criteria

50 consecutive HIV positive patients reporting to the hospital OPD or admitted in the hospital were taken as study group. 50 age and sex matched HIV negative patents were included as controls. Informed consent was taken from study and control groups. Inclusion criteria:

Exclusion criteria:

1. Withdrawal of ART and evidence of clinical signs of active AIDS in the 3 months before entry because of their possible impact on anthropometric, blood pressure and laboratory parameters.
2. Established coronary heart disease and other atherosclerosis related diseases.
3. Patients with type 2 Diabetes.

Method of evaluation:

The study was carried in a tertiary care hospital. It was performed over a period of two years from Jan 2017 to Jan 2019.The study population was divided into two major groups; test group (HIV/AIDS patients) and the control group. The test group was further subdivided into two sub groups, one on ART and other not on ART. The type and duration of ART was recorded.

All patients were subjected to Colour Doppler flow imaging of carotid vessels using high end Doppler equipment (GE, Logiq P5). Both Gray scale and Colour Doppler imaging carried out using linear 7.5 to 10 MHz probe. The patients were placed in a supine position after at least 10 minutes of acclimatization in a comfortable room. They were informed that the investigation was non-invasive and informed consent was taken.

The common carotid artery (CCA), the bifurcation of carotid artery and proximal (at least the first 2 cm) of the internal (ICA) and external carotid vessels (ECA) were examined on either side in the short and long axes using appropriate magnification settings. This was done to minimize errors of measurements at low magnification settings. (Figure 1) The intima-media thickness (IMT) was measured at 3 places carotid bulb, Internal carotid artery (ICA) and CCA on either side. The CCA was measured at 1 cm proximal to dilatation of carotid bulb. The carotid bulb was measured at 1 cm proximal to carotid bifurcation. The ICA was measured at 1 cm distal to bifurcation of carotid. The IMT of the far wall of carotid was taken. An arithmetic mean of all the 6 values was derived per each subject.

Pathological IMT is defined as mean IMT more than 0.8 mm.(10) Atherosclerotic plaque is defined as an area of thickening with IMT more than 0.12mm irrespective of presence or absence of calcification (11) . A plaque showing calcification is defined as hard plaque and not showing calcification as soft plaque.

The grey scale characteristics of the intima, the Pulsatility index (PI), resistance index(RI), End diastolic velocity (EDV), Peak systolic velocity(PSV) and mean velocity were also measured. Atherosclerotic plaques when present were described.

Comparative statistical analysis within the two groups and within the sub groups was done by calculating the Mean, Standard Deviation, Standards error of mean, 95% confidence intervals. Student's t test was used to calculate the statistical significance of difference in means. Head to head comparison between HIV patients and controls; ART and non-ART groups; non ART and control groups were done. The investigator was not blinded as he knew the HIV status of the subject before performing the assessment.

RESULTS

Test group (HIV positive):
Total of 50 patients of HIV positive patients (test group) meeting the inclusion criteria were included in the study. 40 out of them were male and 10 were females. 35 of them were on ART and 15 of them were not on ART. All the patients received combination ART (zidovudine/ stavudine+ lamivudine+nevirapine/efavirenz). Mean duration at the time of entry into study was 2.88y (1-5y). 13 of them have been on ART for less than 2 years. Average age of population was 35.2 years (23 to 46 years).

The mean IMT in the test group was 0.746 mm with a standard deviation of 0.181 and SEM of 0.026. 14 out of 50 patients showed pathological IMT (> 0.8 mm). The prevalence of sub clinical atherosclerosis in the test group was 28% (17- 41, 95% CI). One of the patients in the test group showed a soft plaque. The prevalence of plaque was 2%.(0.3 – 10, 95% CI)

ART sub group:

Further analysis of the sub groups within the test group was done. A total of 35 HIV patients were on ART. Average age of this ART given sub group was 37 with a range of 28 to 46.

The mean IMT in this ART given sub group is 0.817 mm with a standard deviation of 0.167 and SEM of 0.028. 14 out of 35 patients showed pathological IMT (> 0.8 mm). The prevalence of sub clinical atherosclerosis in the test group was 40%(25-56, 95% CI). One of the patients in this sub group showed a soft plaque. The prevalence of plaque was 2.8%(0.5-14, 95% CI).

Non ART sub group:

A total of 15 HIV patients were ART naïve (ART not given). Average age of this ART naïve sub group was 31 with a range of 23 to 38. The mean IMT in this ART naive sub group was 0.58 mm with a standard deviation of 0.068 and SEM of 0.017. None of the patients had pathological IMT thickening or plaques (prevalence of 0% with 95% CI of 0-20%).

Control group (HIV negative):

A total of 50 healthy age and sex matched controls were enrolled in the study. The control group included 40 males and 10 females. The mean age was 35 with a range of 24 - 44 years. The mean IMT in the control group was 0.572 mm with a standard deviation of 0.101 and SEM of 0.014. None of the patients in this sub group had a pathological IMT thickening or a plaque. (prevalence of 0% with a 95% CI of 0-7%).

HIV patients Vs Control group:

The difference in mean IMT of these two groups was 0.174 (The 95% confidence intervals 0.116 to 0.232). This difference is statistically very significant with a p value of <0.001.

ART group vs non ART group:

The difference in mean IMT of these two groups was 0.237 (The 95% confidence intervals 0.147 to 0.327). This difference is statistically very significant with a p value of <0.001

Control Vs non ART (HIV positive) group:

The difference in mean IMT of these two groups was -0.008 (The 95% confidence intervals -0.064 to 0.048). This difference is statistically not significant with a p value of 0.7751.

DISCUSSION

The association between HIV, ART and carotid IMT is not well established. There were few studies which suggested that HIV infected people have higher IMT. Some large multicenter trials like DADS trial suggested that Combination ART is significantly associated with higher baseline IMT.

HIV and Mean IMT:

The mean carotid IMT (0.74 mm) in HIV positive group is significantly higher than the mean carotid IMT that of controls (0.57 mm). Similarly, in a study by Grunfeld et al. the mean IMT in HIV positive group was 1.17 mm as compared to 1.06 in controls.(12) In another study by Hsue et al. mean carotid IMT was 0.91 mm in HIV patients as compared to 0.74 mm in control group.(13) In a study by Coll et al. the baseline IMT was 0.75 mm and was significantly higher.(10)

Though the trend of higher IMT in HIV positive group correlated with our results, there are individual variations in the mean IMT in individual studies. This could be due to differences in the site and technique of measurement of IMT, difference in the mean age of population.

Prevalence of Sub clinical atherosclerosis and HIV:

The prevalence of sub clinical carotid atherosclerosis in HIV population was significantly higher (28%) than control group (0%). Similarly, in a study by Jerico C et al. (6) the prevalence of sub clinical atherosclerosis was 41% in HIV positive group of 132 patients. The difference in the prevalence could be due to differences in the definition of plaque, mean age of the study population and the type and duration of ART.

ART sub group and sub clinical atherosclerosis:

The data from our study shows that IMT was higher in ART sub group (0.81 mm) as compared to Non ART sub group (0.58 mm). The prevalence of sub clinical atherosclerosis (presence of pathological IMT thickening or plaque) was also higher in ART sub group (40%) than Non ART group (0%). Similarly, in a study by Seminari et al. the IMT was higher in HIV patients with exposure to Protease inhibitors as compared to HIV patients without exposure to PIs.(14)

The most important factor affecting the strength of association between ART and subclinical atherosclerosis the duration and type of ART given. Sub clinical atherosclerosis being a cumulative disease, the prevalence would increase with duration of ART. Few studies have shown that especially Protease inhibitors are associated with much higher carotid IMT. Due to small size of the population (35 cases) further analysis of influence of duration and type of ART and its influence on carotid IMT was not attempted in our study.

Limitations:

The study had a few limitations. As a cross sectional observational study, it only represents the influence of various factors on carotid IMT at the time of observations. This may not match with the cumulative influence of these factors. The small sample size of this study limits the statistical power of the observations. The study population may not be an accurate representation of the general population. Further the inherent limitation of being an observational study precludes assigning a causal relationship between HIV disease, ART treatment with increased carotid IMT.

CONCLUSIONS

HIV positive patients (including both treatment naïve and treated with ART) are associated with higher carotid IMT. Treatment of HIV patients with combined ART is associated with further higher carotid IMT inferring an increased prevalence of sub clinical carotid atherosclerosis in this population. There seems to be no statistically significant difference in the carotid intimal medial thickness between Non ART HIV patients and healthy controls.

Conflicts of interest

None.

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