Acanthosis nigricans in patients with HIV infection and its relation to metabolic syndrome

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BACKGROUND: Insulin resistance (IR) plays a major role in the pathogenesis of metabolic syndrome. Acanthosis nigricans (AN) is an easily detectable skin condition that is strongly associated with IR. The aims of this study were, firstly, to investigate the prevalence of AN among people living with HIV/AIDS in western India and its relation to metabolic syndrome.

MATERIAL AND METHODS: This study was a cross sectional, single center, observational study of 18 months duration from January 2017 through June 2018. PLHA attending Anti-retroviral Therapy (ART) clinic or admitted at a tertiary care centre in Western India were included in the study. Sample size of 300 was chosen for this study.

AN was defined as presence of velvety, hyperpigmented plaques on the skin. MS was defined by NCEP ATP III criteria. Serial HIV-positive patients attending ART clinic or admitted to the hospital were screened for presence of AN. Relevant anthropometric measurements of study subjects were recorded. Skin was examined for presence of AN and the same was recorded. The laboratory parameters measured included fasting and post prandial blood glucose, total cholesterol (TC), HDL-C, low density lipoprotein-cholesterol (LDL-C), and Triglycerides (Tg).

FINDINGS: In a tertiary care hospital in OPD and IPD settings adults patients underwent, clinical examination, biochemical and serological tests. 299 subjects were included in this analysis. The prevalence of AN and MS was 13.7% and 12.7% respectively. There was a strong association between AN and metabolic syndrome. The sensitivity, specificity, positive predictive value and negative predictive value of AN to detect MS to be 17.07%, 87.98%, 18.42% and 86.97% respectively.

CONCLUSION: Acanthosis nigricans is a common and easily accessible dermatological condition. Increased waist circumference and WHR are strong predictors of AN. AN can be used to predict occurrence of MS with high specificity and patients should be thoroughly evaluated for MS in its presence.

Key Words: *Tumour; Urinalysis; Glucose; Clinical diagnosis; Acanthosis nigricans*

INTRODUCTION

The burgeoning epidemic of obesity and diabetes will be the defining features of healthcare challenges in the 21st century. Worldwide, the proportion of adults with a body-mass index (BMI) of 25 kg/m^2 or greater increased between 1980 and 2013 from 28·8% (95% UI 28·4–29·3) to 36·9% (36·3–37·4) in men, and from 29·8% (29·3–30·2) to 38·0% (37·5–38·5) in women. Prevalence has increased substantially in children and adolescents in developed countries; 23·8% (22·9–24·7) of boys and 22·6% (21·7– 23·6) of girls were overweight or obese in 2013. The prevalence of overweight and obesity has also increased in children and adolescents in developing countries, from 8·1% (7·7–8·6) to 12·9% (12·3–13·5) in 2013 for boys and from 8·4% (8·1–8·8) to 13·4% (13·0–13·9) in girls (1). According to the National Family Health Survey (NFHS) of India, the percentage of ever-married women aged 15-49 years who are overweight or obese increased from 11% in NFHS- 2 to 15% in NFHS-3 (2). In India, many studies have shown that the prevalence of overweight among adolescents varies between 10% and 30% (3). There is marked geographical variation in prevalence of diabetes. The prevalence is lowest in rural areas of developing countries, it is generally intermediate in developed countries, and is highest in certain ethnic groups, particularly those that have adopted Western lifestyle patterns. The number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014. The global prevalence of diabetes among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014 (4). Prevalence of diabetes in India is 8.8% according to International Diabetes Federation (IDF).

It is estimated that the onset of diabetes occurs an average of about 4-7 years before clinical diagnosis based on symptoms, and that one-third to one-half of individuals with type 2 diabetes are undiagnosed at any given time (5). In the general population, several metabolic risk factors are strongly interrelated and are part of the metabolic syndrome (MS). This was elegantly described by Reaven in 1988 (6). MS is a constellation of derangements in glucose, insulin, and lipid metabolism, along with abdominal obesity. The National Cholesterol Education Program (NCEP) has endorsed the importance of MS in cardiovascular risk assessment by introducing a case definition of MS based on clinically easily obtainable anthropometric and laboratory parameters (7). MS affects 24 percent of the adult population in the U.S. and 15 percent of non-diabetic adult Europeans and is associated with an increased risk of CVD (8,9). MS is associated with abdominal obesity, but absolute or partial lack of body fat may result in a similar metabolic risk profile. It is therefore important to recognize markers of insulin resistance and be proactive in advising lifestyle changes to obese individuals with these markers and also keep them under follow up for introduction of drug therapy for diabetes as soon as it clinically manifests.

Acanthosis nigricans (AN) is one such marker of insulin resistance which is easy to detect. However there are not many studies which have correlated this ubiquitous clinical marker with metabolic syndrome. And moreover there is no study on people living with HIV/AIDS (PLHA). It is particularly relevant in this population where both the disease and its treatment predispose to dyslipidemia and where in future the highest cause for mortality will be cardiovascular disease. This study was designed to address this gap in knowledge and estimate the prevalence of acanthosis nigricans in PLHA, it shows in Figure 1 and see its correlation with occurrence of MS.

STUDY DESIGN AND METHODOLOGY

This study was a cross sectional, single center and observational study. The duration of the study was 18 months from January 2017 through June 2018. PLHA attending Anti-retroviral Therapy (ART) clinic or

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Figure 1) *Acanthosis nigricans observed in the axilla of patient with HIV in OPD*

admitted at a tertiary care centre in Western India were included in the study. The prevalence of MS in PLHA varies from 7 – 45%. An Indian study showed prevalence of 20% in PLHA (10). AN is seen in 28-70% cases of MS (11,12). For calculation of sample size a prevalence of 15% & 40% was taken for MS and AN respectively. Expected Prevalence of AN in MS was 6% (40% of 15%). Sample size was calculated with the help of the website www.sample-size.net. It was found that for the expected result of 6% (range 3-9%) with 95% confidence level, a sample size would be 271. Therefore a sample size of 300 was chosen for this study. All adult patients (>18 yrs) with HIV infection attending ART clinic or admitted to a tertiary care centre in Western India were eligible for inclusion in the study. Patients on corticosteroid therapy, those diagnosed with diseases of adrenal gland and known thyroid dysfunction including tumour or surgery were excluded from the study.

AN was defined as presence of velvety, hyperpigmented plaques on the skin. MS was defined by NCEP ATP III criteria in which presence of three or more of following was diagnostic of MS (i) Abdominal obesity, given as waist circumference Men > 102 cm and Women >88 cm (ii) Triglyceride (Tg):> 150 mg/dl Men > 102 cm and Women >88 cm (ii) Triglyceride (Tg):> 150 mg/dl (iii) HDL Cholesterol (HDL-C): Men <40 mg/dl and Women <50 mg/dl (iv) Blood pressure (BP): >130/>85 mmHg and (v) Fasting plasma glucose (FPG):>110 mg/dl. Serial HIV-positive patients attending ART clinic or admitted to the hospital were screened for presence of AN. Written informed consent was taken from all the patients before enrolling them in the study. Anthropometric measurements of study subjects that were measured and recorded included height, weight, BMI, waist circumference, and hip circumference. Waist circumference was measured midway between the iliac crests below and subcoastal margins above. It was done using a flexible measuring tape. Hip circumference was taken at the level of the greater trochanters. Skin was examined especially in neck, axilla, knuckles, cubital and popliteal fossae and other intertriginous areas for presence of AN and the same was recorded The laboratory parameters measured included fasting and post prandial blood glucose, HbA1c in selected cases, Total cholesterol (TC), HDL-C, low density lipoprotein-cholesterol (LDL-C), and Triglycerides (Tg). The results of complete blood counts (CBC), renal function tests (RFT), liver function tests (LFT) and urinalysis were noted from patient records if they had been done within the past three months. Otherwise, fasting samples were drawn the next day. The subjects were screened for presence of MS based on NCEP ATP-III criteria.

STATISTICAL ANALYSIS

The data on categorical variables is recorded as n (% of cases) and the data on continuous variables is presented as mean and standard deviation (SD). The inter-group comparison of categorical variables is done using Chi-square test. Sensitivity, specificity, positive predictive and negative predictive values were calculated with the help of 2 x 2 contingency tables. All the results are shown in tabular as well as graphical format to visualize the statistically significant difference more clearly. For this study, p-values less than 0.05 are considered statistically significant. Strict compliance to patient confidentiality was maintained. Clearance from institutional ethical committee was taken.

RESULTS

Acanthosis nigricans was seen in 41 patients i.e., 13.7% of the total enrolled subjects. It was more common in males as compared to females (15.35 vs. 9.52%) though the difference was not statistically significant. All the patients were divided in two groups: those with AN and those without it. The t test was used to look for association between various clinical parameters and AN. Mean BMI was found to higher in patients with AN and this was statistically significant (p=0.045). However mean age, CD4 counts, duration of disease, duration of therapy and ART regimen were not found to be significantly different between the 2 groups. MS was found in 38 patients (12.7%) in our study population. The patients with MS (n=38) were divided into two groups on basis of presence (7/38) or absence (31/38) of AN, comparison of these two groups revealed that patients of MS with AN were older (Mean ± SD 49.29 ± 10.77) than those without (41.52 ± 9.80). The BMI was also higher in subjects with MS and AN when compared to those with MS but without AN (27.35 vs. 25.36 kg/m^2). However this finding was not statistically significant

Significantly higher waist circumference (97.4 vs. 86.5 cm) and WHR (1.05 vs. 0.94) were noted in subjects with MS and AN when compared to those with MS but without AN (p-value < 0.03 and 0.005 respectively). This is shown in Table 1.

TABLE 1

Patient demographics of foreign-born HIV patients based on continent of origin in the Parkland Hospital system in Dallas, Texas from 2010-2016.

Variables	Acanthosis in subjects with metabolic syndrome (N=38)			
	Present mean (SD)	Absent mean (SD)	P-value	Significance
Age	49.29 (10.77)	41.52 (9.80)	0.071	No
BMI (kg/m^2)	27.35 (4.56)	25.36 (4.37)	0.287	No
Waist	97.43 (10.64)	86.55 (11.64)	0.03	Yes
WHR	1.05 (0.11)	0.94 (0.08)	0.005	Yes
Males	4 (10.5%)	23 (60.5%)	NA	NA

N=Number of patients

Waist circumference was more in patients of AN irrespective of presence or absence of MS and this indicates that abdominal obesity is an independent risk factor for AN. Both waist circumference and WHR are significantly associated with AN in patients with MS however the number of subjects in this subset was low (n=38). as depicted in Table 1 and 2.

Variables	Acanthosis in subjects without Metabolic syndrome (n=261)			
	Present mean (SD)	Absent mean (SD)	P value	significance
Age	41.62 (9.8)	41.12 (12.10)	0.82	No
BMI (kg/m^2)	23.60 (4.56)	22.41 (4.37)	0.136	No
Waist	85.44 (8.9)	81.75 (9.66)	0.037	Yes
WHR	0.92 (0.08)	0.92 (0.07)	0.73	no
Males	29 (11.1%)	159 (60.9%)	0.065	no

Sensitivity and specificity analysis of AN and MS revealed high specificity (87.98%) of AN in predicting MS and a high negative predictive value (86.97%). But there was low sensitivity of AN in predicting presence of MS (17%) and low positive predictive value (18.42%).

DISCUSSION

MS is a common complication in patients of HIV with prevalence rate varying from 12 - 40% (13-16). AN is frequently seen in cases at risk of MS. However, prevalence of AN and its utility for diagnosing MS is not well known in patients with HIV infection. This study was conducted with primary objective of finding the prevalence of in patients of HIV, and its relation with MS. Previous studies have reported a highly varied prevalence of in different ethnic groups, dark skinned people being more commonly affected than the fair skinned. Stuart et al. for the first time reported the prevalence of AN in an unselected population. The prevalence was 7% in adolescents and varied from 30%–40% in adults (17). Dassanayake and colleagues found a prevalence of 17% in an

urban population in Sri Lanka (11). Grandhe et al. found a significantly higher prevalence of AN among Indian diabetic patients (62.6%) when compared with healthy subjects (40%) (18). The highest prevalence of AN (74%) was reported by Hud et al. in a subset of obese population (19). The prevalence of AN found in our study was within the range described in different populations in past studies. However, it is perhaps the first study on prevalence of AN in HIV patients to the best of our knowledge.

Many studies have been conducted on MS in patients of HIV infection. The prevalence rates of MS in HIV patients in published studies vary from 10.1% to 45.4%. Various Indian studies have reported prevalence of MS in general population between 3% and 25% (20). The prevalence of MS found in our study was 12.7% which is within the described range.

Dassanayake et al. in Sri Lanka investigated the prevalence of AN among adults in an urban Sri Lankan community and described its utility to detect MS. The sensitivity, specificity, positive predictive value and negative predictive value of AN to detect MS were 28.2%, 89.0%, 45.9% and 79.0% for males, and 29.2%, 88.4%, 65.6% and 62.3% for females, respectively (11). Another study was done in Chennai in India to estimate sensitivity and specificity of AN as a skin marker of MS. This study had very stringent exclusion criteria. Subjects with history of diabetes, hypertension, dyslipidemia and alcohol consumption were excluded. The sample size was hundred. The prevalence of MS in their population was very high compared to our study. It was 48%. For detecting MS, AN had a sensitivity of 62.50% (48.36, 74.78), specificity of 94.23% (84.36, 98.02), positive predictive value of 90.91% and negative predictive value of 73.13% (21).

In our study we found sensitivity, specificity, positive predictive value and negative predictive value of AN to detect MS to be 17.07%, 87.98%, 18.42% and 86.97% respectively. The sensitivity to detect MS was found to be lower in our study. However, the negative predictive value found in our study was significantly higher. These results were similar to ones reported by Dassanayake et al, but contrary to the findings of the Chennai study. In comparison with study done by Balaji et al. (Chennai study) we found lower prevalence of AN and MS and similar specificity and negative predictive value. However sensitivity was lesser 17.07% vs. 62.5%. The difference in prevalence of AN and MS may be due to major inherent difference in the two study populations. MS in patients with HIV has been described in only 3-20% of cases in India but in the study conducted at Chennai prevalence MS was reported as high as 46% (21). The difference between these studies in sensitivity may be attributable to much larger sample size of our study population (300 vs. 100) and lower prevalence of AN and MS 13.7 vs. 33% and 12.7 vs. 48%.

STRENGTHS

There are very few studies on prevalence of AN in general population in India. We could find only one study in India which evaluated significance of AN as a marker of metabolic syndrome. The sample in this study was 100. In our study we used a much larger sample size. There is no study on AN in patients with HIV infection. Ours is a novel study in this regard. AN and MS were found to be fairly common in our study population, (13.7 and 12% of cases respectively). AN was found to predict MS with a very high specificity.

LIMITATIONS

Our study had a few limitations. Firstly, AN was not quantified using a standard scale and only its presence or absence in the neck was noted, this might be a subject for future studies. Secondly, NCEP ATP 3 criteria was used for diagnosis of metabolic syndrome. Since it was done on Indian patients, South Asian modification of NCEP ATP 3 could have been more appropriate diagnostic criteria. Lastly, as this study was carried out at a military hospital, findings may not be generalized as service personnel or veterans are generally fitter and have a more active lifestyle.

RECOMMENDATION/EXTRAPOLATION

In this study it was found that AN and MS was fairly common in patient with HIV infection. WHR and WC were found to have a strong predictive value for AN. WC was shown to be a predictor of AN even in absence of MS. AN when used as a clinical tool to predict occurrence of MS showed a high specificity and high negative predictive value but low sensitivity.

Patients with AN are at risk for all components of the MS such as obesity, hypertension, elevated triglycerides, low HDL, and impaired glucose tolerance. Since AN can be easily picked up on clinical examination, it has potential to detect people at risk for MS. This is especially relevant in South East Asia where both obesity and MS are acquiring epidemic proportions. It is also a good clinical marker for MS in resource- poor settings where access to laboratory may be difficult.

CONCLUSION

Acanthosis nigricans is a common and easily accessible dermatological condition. Increased waist circumference and WHR are strong predictors of AN. AN can be used to predict occurrence of MS with high specificity and patients should be thoroughly evaluated for MS in its presence.

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