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Acanthosis Nigricans in Adolescents versus Adults; Association with Obesity, Diabetes and Hypertension

Furquana Niaz, Nadia Shams, Naresh Kumar, Irfan Sheikh, Nayer-ul-Islam, Najia Ahmed

ABSTRACT:

Objectives: Acanthosis nigricans presents as black velvety plaques on flexural surfaces which is associated with obesity, T2DM and HTN. To study sites and types of AN (Acanthosis Nigricans) in adolescents Vs. adults and its associations.

Study design & setting: This cross sectional study was conducted from IstMar-31stAug 2021 at RIHS Islamabad after ethical approval.

Methodology: Adolescents and adult cases of both the genders with AN were *included* by convenience sampling. Critically ill cases, endocrine disorders, pregnancy and malignancy were *excluded*.57 adolescents and 57 gender matched adults were included. After the detailed clinical evaluation, BMI, waist circumference, sites and types of AN were documented. Blood sugars and workup for PCO's, suggested. Data was analyzed by SPSS 21. Chi-square test and Mann-Whitney-U test applied.

Results: Out of 114 cases,77(67.5%) were females. The mean age was 17.99+14.18 years and mean BMI was 31.63+6.92 kg/m^2.Obesity was observed in 75(65.8%); 44(77.2%) adolescents Vs. 31(54.4%) adults *(p=0.010).* Mean waist circumference was 37.03+3.74 inches.AN at Neck 113(99.1%) and benign AN 111(97.4 %) were the most frequent. The types of AN were associated with obesity, DM 31(27.2%) and HTN 27(23.7%) ($p<0.05$).

Conclusions: Benign and HAIR-AN were most frequent. Adolescents with AN have significantly higher obesity than adults. HTN was significantly higher in adults. DM in AN was observed regardless of age group. It is suggested to screen all AN cases regardless of age or gender for obesity, HTN and DM. Early diagnosis may contribute to improve quality of life, prevent morbidity of systemic diseases and improve outcome in AN cases.

Keywords: Acanthosis nigricans, BMI, HAIR-AN syndrome, Obesity, PCO

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INTRODUCTION:

Acanthosis nigricans (AN) is an asymptomatic skin condition which presents as brown/black rough velvet like thickening of skin that involves intertriginous areas and mucosal surfaces including oral mucosa, lips, conjunctiva and vulva.[1-3] Dr. Paul & Pollitzer documented the 1st case of AN[1,4], while Robinson & Tasker documented its relation with obesity. The prevalence of pediatric obesity from 2-19 years of age is 10.4%-15.5 and in male children is 26.7% and 34.6% in females which increases risk for DM.[1,5] The prevalence is 62% in children of any race with BMI>98th percentile and in adolescents 66% with gross weight of more than 200%.[1,4] The American Medical Association (AMA) declared obesity to be "A category disease".[5]

AN can present from birth to adolescence that impact on health of individuals[6] and causes psychological disturbance due to unsightly appearances.[5] Stuart et al proposed Acanthosis score in literature ranging from 0 to 4, based on degree of involvement while Hud et al provides severity of AN on the basis of texture. Burke et al proposed a visual scale for severity of AN on neck and its correlation with BMI. Kobaissi et al criteria was based on severity of AN.[5]

The three classifications of the types of AN include [2]Curth

classification (benign, malignant and syndromic AN), Hernandez-Perez (simple and paraneoplastic AN), Schwartz classification (Benign, associated with obesity, unilateral, syndromic, mixed, drug induced, acral and malignant AN).[2]

Benign AN is associated with IR.[1]Obesity associated AN is associated with obesity in prepubertal children. Among children and young child at risk for overweight if BMI > 85th percentile but < 95th percentile for that age but if BMI till 95th percentiles are consider as overweight.[7]This can be indicator of obesity, hyperinsulinemia, IR and T2DM and detected by increased WC .[6]AN may appear prior to obesity[5] Obesity in adolescence increases the risk of heart diseases.[8]Regarding pathogenesis of AN, hyperinsulinemia leads to activation of IGF that causes proliferation of dermal fibroblast and epidermal keratinocytes. Friction and sweating may also causes AN.[6]Obesity causes negative stereotypes on cognitive functions and intelligence .Weight bias, stigmatization and discrimination which leads to physical and psychological hazards.[5]

The type A insulin resistance syndrome (HAIR-AN syndrome).[1]is associated with PCO.[1,4,9]The type B insulin resistance syndrome presents as periocular AN.[1,4]Acral AN is associated with NFP and dermato-fibrosarcoma.[1]The Unilateral/Neavoid AN has no associations.[1]Facial AN could be manifestation of impaired glucose tolerance, increase waist hip ratio and BMI. Mixed type AN, if >1 type of lesions are present in one patient. Drug induced AN is caused by nicotinic acid, OCP, corticosteroids and fucidic acid.[1,4]The Malignant AN is associated with gastric carcinoma[4]presents with Tripe palms.[8]

Obesity can be associated with AN and MetS like IR, hyperinsulinemia, acne, T2DM, PCOs, HTN and dyslipidemia.[2,3,5,9,10] AN is a good clinical indicator for impaired glucose tolerance. American Academy of pediatrics suggested AN being the evidence of IR clinically while ADA recommended AN as a risk factor for cardio metabolic problems in asymptomatic overweight children.AN in the neck and axillae is non-invasive, valuable and simple screening tool to determine T2DM and other comorbidities.

Obesity leads to risk of high BP and BMI is a good indicator for obese and overweight.[7]So far, very few local studies are available regarding AN associated with obesity (increased BMI and WC) HTN and T2DM.In our study we determined the frequency of AN in obese adolescents Vs adults in accordance with BMI and WC. This study will help us to identify the cases of AN to be screened for obesity and its associations like T2DM, HTN on the basis of gender, age and types of AN. Also, this study may help us to develop a clinical approach to diagnose and manage obesity, DM and HTN that are the systemic associations via skin presentation.

METHODOLOGY:

This hospital based cross sectional study enrolled AN cases from outdoor clinic Department of Medicine Rawal institute of Health Sciences Islamabad after institutional review board approval (IRB letter number: RIHS-REC/059/21).Patients were selected by non-probability convenience sampling over five months duration (1st March to 31st Aug 2021).The sample size calculated to be 114 cases by WHO calculator(17.5% prevalence of acanthosis nigricans,5% precision and 95% CI).Cases referred to Medical Department from pediatrics OPD with clinical diagnosis of AN were included after informed consent (from patients and guardian).**Inclusion criteria:** Children & adolescents; both the genders of age group of 10-48 years. **Exclusion criteria:** Critically ill, underlying Addison's disease, pregnancy and malignancy. 57 adolescent AN cases were selected and 57 gender matched adults.

After the detailed history regarding onset, progression and duration of pigmentation and systemic co-morbidities like T2 DM, HTN and PCOS were documented. Dietary habits, drug history, personal, family history inquired. Menstrual and reproductive history were taken in females. General physical, systemic and detailed skin examination (neck, axillae, groin, sub mammary region, palms, soles and all mucous membranes checked) for AN. Weight in kg was measured by platform type digital electronic scale by keeping patients barefoot and height in meters measured by keeping patient upright with united foot. BMI calculated by CDC child and teen BMI calculator in which mentions age in years and months, gender, height in feet and inches/cm, weight in kg/lbs and calculated BMI by formula weigh in Kg/height (m^2). Waist circumference was measured by flexible measuring tape from narrowest part of torso, midway between the lowest rib and iliac crest and noted in inches for central obesity after expiration. Blood pressure was measured in the right arm, at the level of heart in a sitting and resting position. The patients were classified on the basis of BMI as overweight or obese according to their age and height via using criteria by CDC child and teen BMI calculator. Relevant investigations were suggested as per indication in individual cases and data recorded in specifically design proforma.

Data were analyzed by SPSS version 21. Frequency and percentages were calculated for qualitative variables (gender, obesity, co-morbid, type of AN); mean with standard deviation for quantitative variables (age, height, weight, BMI, waist circumference). Shapiro-Wilk test was performed to assess the normality of the distribution of the variables, this showed that our data was non-normal. Chi-square test was used to compare qualitative variables between adolescents and adults. Mann-Whitney-U test was used to compare non-normally distributed continuous variables between two groups. The p-value < 0.05 was considered to be significant.

RESULTS:

In our study total number of cases were 114 in which half

57 were adolescents and half (57) were gender matched adults. There were 77(67.5%) females and 37(32.5 %) males, both groups were comparable with respect to gender *(p=0.841)*. The mean age was 17.99+4.72 (10–48 years range); 14.44+1.80 years(adolescents) Vs. 21.54+3.9 years adults*)(p<0.0001)*. The mean height was 4.99+0.44 feet; 4.88+0.48 (adolescents) Vs. 5.09+0.39 (adults) *(p=0.026)*.The mean weight was 70.66+14.18kg; 66.39+13.02(adolescents) Vs. 74.93+14.12kg (adults) *(p=0.001)*. Mean waist circumference was 36+3.52(range 14-47 inches); 34.91+4.28 (adolescents) Vs. 37.10+2.07(adults) (*p<0.0001)*. As per WHO criteria for adolescents and adults; obesity was seen in 44(77.2%) adolescents with AN Vs. 31(54.4%) adults with AN *(p=0.010)*. Over all, among the 114 cases of AN, 75(65.8%) were obese and 39(34.2%) were non-obese *(fig 1)*

Table 1: The demographic variables, anthropometric measurements, site and types of acanthoses nigricans in adolescents Vs. Adults *(n=114*

VARIABLES	n (%) n=114	Adolescents n=57	Adults n=57	P-value
Age(10-48yrs)	17.99+4.72	14.44+1.80	21.54+3.9	**<0.0001**
Height (3.5-5.9 ft)	4.99+0.44	4.88+0.48	5.09+0.39	**0.026**
Weight (30-120 kg)	70.66+14.18	66.39+13.02	74.93+14.12	**0.001**
Waist circumference (14-47 inches)	36+3.52	34.91+4.28	37.10+2.07	**<0.0001**
Obesity				
Obese	75(65.8%)	44(77.2%)	31(54.4%)	**0.010**
Non-obese	39(34.2%)	13(22.8%)	26(45.6%)	
Gender				
Females	77(67.5%)	39(68.4%)	38(66.7%)	0.841
Males	37(32.5%)	18(31.6%)	19(33.3%)	
Site of AN				
Neck	113(99.1%)	57(100%)	56(98.2%)	0.315
Groin	88(77.2%)	43(75.4%)	45(78.9%)	0.655
Knuckles	61(53.5%)	28(49.1%)	33(57.9%)	0.338
Axilla	55(48.2%)	23(40.4%)	32(56.1%)	0.123
Sub-mammary	59(51.8%)	26(45.6%)	33(57.9%)	0.190
Types of AN*				
HAIR AN	61(53.5%)	32(56.1%)	29(50.9%)	0.573
Acral	14(12.3%)	05(8.8%)	09(15.8%)	0.302
Mixed AN	01(0.9%)	0(0%)	1(1.8%)	0.315
Unilateral AN	0(0%)	0(0%)	0(0%)	-
Syndromic	2(1.8%)	0(0%)	02(3.5%)	0.154
Benign AN	111(97.4%)	56(98.2%)	55(96.5%)	0.558
Diabetes mellitus				
Diabetic	31(27.2%)	14(24.6%)	17(29.8%)	0.528
Non-diabetic	83(72.8%)	43(75.4%)	40(70.2%)	
PCO (n=77 females)	62(80.5%)	30(76.9%)	32(84.2%)	0.707
Hypertension	27(23.7%)	6(10.5%)	21(36.8%)	**0.001**
Autoimmune	36(31.6%)	13(22.8%)	23(40.4%)	**0.044**
Drug induced	0(0%)	0(0%)	0(0%)	-
Familial	0(0%)	0(0%)	0(0%)	-

Regarding site of AN, neck was the most common site 113(99.1%). This was followed by groin 88(77.2%),knuckles 61(53.5%),sub-mammary region 59(51.8%) and axillae 55(48.2%)*(fig. 2)*. and Regarding types of AN, the benign type was most common i.e., found in 111(97.4%) in our study; 56(98.2%) in adolescents and 55 (96.5%) in adults *(p=0.558)*,followed by HAIR-AN syndrome 61(53.5%) and acral AN 14(12.3%).Only 2(1.8%)syndromic types and one case of mixed type were noted in our study. Not a single case reported of unilateral variety in our study. Regarding associated conditions and co-morbid, DM observed in 31(27.2%) AN cases and 83(72.8%) AN cases were non-diabetic. Diabetes was seen in 14(24.6%) adolescents Vs. 17(29.8%) adults *(p=0.528)*. PCOs seen in 62(80.5%) out of total 77 females with AN with no difference between adolescents and adults (p>0.05). Hypertension were seen in 27(23.7%)cases of AN, hypertension was much more common in adults with AN 21(36.8%)Vs. adolescents 6(10.5%) *(p=0.001)*.Autoimmune conditions were seen in 36(31.6%) AN cases and no case were found of drug induced and familial variety of AN.

Fig 1: Bar graph representing sites of Acanthosis Nigricans in Adolescents Vs. Adult cases (n=114)

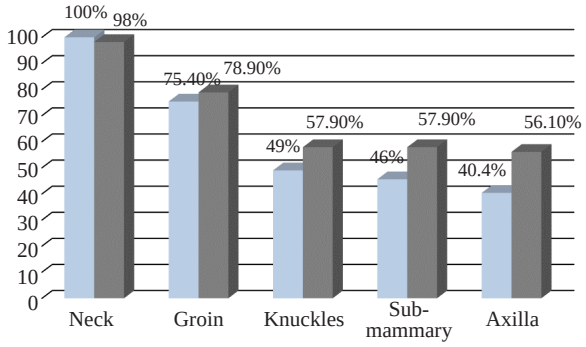
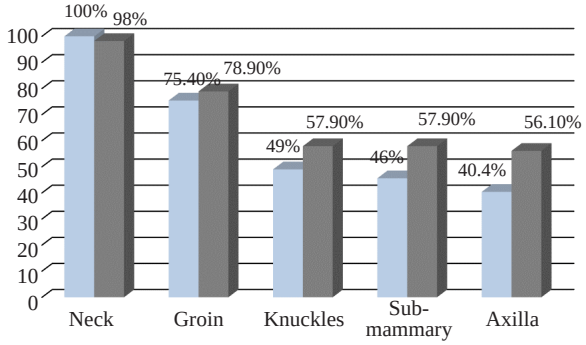


Fig 2: Bar graph presentation of various type of acanthosis nigricans in Adolescents Vs. Adults (*n=114*)



DISCUSSION:

AN is a skin condition that is featured by brown/black velvety plaques in skin folds and associated with syndromes, hereditary disorders, DM, Hypothyroidism, Addison's disease ,Cushing Syndrome and hypogonadal syndromes.[6,11] Prevalence of AN varies from 74% in Obese persons and 7% involves unselected population.[12] AN acts as skin marker for malignancy, IR and metabolic syndromes(Mets)in overweight/obese children and adolescents.[13,14] AN secondary to obesity is related to IR, increased insulin level in the blood.[15,16] The pediatric obesity is related to increased risk of prevalence and incidence of T2DM in childhood which is associated with higher risk of micro(nephropathy, retinopathy and neuropathy)and macrovascular complications (like myocardial infarction and stroke).[17]

In our study, we took 114 patients in which 57 were Adolescence and adults in each group. The age range was 10-48 years. Out of 114, 75 (65.8%) were obese in which 44 (77.2%) were adolescent and 31 (54.4%) were adults; obesity was more in adolescents than adults.

Regarding gender in our study, we had 77 (67.5%) females in which 39(68.4%) were adolescent females and 38(66.7%) were adult females. There were 37(32.5%) adolescent males and 18(31.6%) adult males, our study had more females than males presenting with AN. Study by Munise daye showed more obese females as compared to males in their study[15] Study conducted by Wolters Kluwer had same findings, i.e., more females than males. The ratio was 2:1.[2] In our study, the mean BMI was 31.63 ± 6.92 while more in adolescents 34.4 ± 6.92 than in adults 26.45±2.66 but the difference in BMI was not statistically significant *(p>0.05)*. In study by Ashraf, [11] the mean BMI was same as in our study i.e., 31.8 ± 3.9.

Regarding obesity, among 75(65.8%) obese cases as per criteria of BMI by WHO, we observed obesity in 44(77.2%) in adolescents and 31(54.4%) in adults (p=0.010) that is quite significant. While Prakash found 47% obesity in adults in his study that is slightly higher than our study.[2] Generally, obesity is a result from imbalance of energy when intake exceeds from requirement of body. However, it is a complex problem that results from genetic predisposition, environmental factors, human behavior and policy interventions but furthermore, gut flora, epigenetic modifications, viral infections and some psychological factors may also be involved in the pathogenesis of obesity in childhood and adolescents. Previous studies suggested that obesity in childhood exerts adverse effects on health throughout life if not tackled in childhood and cardiovascular risk can be minimized if obese adolescent becomes a nonobese adult.[5]

Regarding Waist circumference, we found this to be 37.03 ± 3 inches in our study. In adults it was 37.7±4.25 and in adolescents 35.769±1.93 inches. A study by Shiva Prakash[18] found mean WC 27(50%) in patients with AN. The WC shows the central obesity and cut off for Asian females is 80cm while in males is 85cm. There is an increased prevalence of AN if WC is 90cm or above. Similarly, decreased occurrence of AN if WC = 90 cm. Hence, if patients have BMI 30 kg/m2 or more than that with WC 90 cm or above he may have AN as a marker for IR. Obesity is a known risk factor for the T2DM & IR.[19,20]Waist circumference is a cost-effective measure, this is not only the good anthropometric measurement to detect abdominal obesity but also an independent guider for insulin resistance.

IDF suggests children of age group of six years, the 90th percentile as a waist circumference but hasn't explained the waist circumference cut off point for less than six years of age in children. Previous studies in the US suggested use of waist circumference for insulin resistance or metabolic syndrome or cardiovascular risk rather than BMI in clinical settings. Studies in the US on children and adolescents suggested cardiovascular risk for waist circumference cut off point at 94th percentile for boys and for girls at 84th percentile. A single measurement of waist circumference cut point in different genders and ethnic groups may be easy to apply but less sensitive to diagnose metabolic syndrome in children.[7]

Regarding the site of AN, out of 114 patients we found the commonest site of AN is neck in 113 (99.1%) cases in which 57(100%) in adolescence & 56(98.2%) in adults (P=0.315). Study by Hasan A Kobaissi found neck involvement in 131(73%) subjects with AN which showed more neck involvement in patients with AN than we found in our study.[20] Nisha[2] found more neck involvement which coincides with our results. Neck involvement was followed by groin 88 (77.2%), 43 (75.4%) in adolescence and 56 (98.2%) in adults (P=0.655), knuckles 61 (53.5%) and axilla in 55 (48.2%). Study by Rodriguez found knuckles, the commonest site of AN (21.6%). The results did not match with our study while Rodriguez found knuckles is a positive value for specificity of AN while detecting HOMA-IR levels more than 90th percentiles in their study.[21]

The neck involvement is the most common site in children and maximum involvement of neck and axillae is due to perspiration or friction and these two sites are the indicator of metabolic risk. Mechanical trauma may be important cause for proliferation of epidermal keratinocytes.[22] Helaisa Marcelina found neck, the most common site (93-99%) followed by axillae (73%).[6,]

Regarding types of AN, out of 114, Benign AN was found in 111(97.4%), the most common type in our study which is followed by HAIR–AN syndrome (includes high insulin resistance, obesity and hyperinsulinemia).[23] Benign type is the indicator for IR secondary to obesity.[24]We found HAIR-AN syndrome, the 2nd most common type 61(53.5%) in which 32(56.1%) were adolescents and 29(50.9%) adults

(p=0.573). HAIR-AN syndrome can be caused by adipose cell dysfunction.[22]

In our study, out of 114, 83(72.8%) were non diabetic and 31 (27.2%) were diabetic, more were non diabetic than diabetic (P=0.523), also more Diabetes in adults than in adolescents in our study. The previous pediatric obesity related studies showed increase incidence and prevalence of childhood T2DM which is not supported to our study. ADA classifies T2DM as a condition caused by progressive loss of beta cells by pancreas that secretes insulin in a person of IR. The ADA recommended for screening of the children and adolescents from 10 years old or above it who are overweight with BMI more than 85th percentiles for that age and sex or obese person with BMI more than 95th percentile for that age and sex. Childhood T2DM is usually developed during puberty and females are more commonly affected than males while age related type T2DM is more common in adult males than females. The cause of this difference is due to increased muscle mass and decreased fat mass in adolescent boys and increased physical exertion and increased sensitivity of insulin in boys than girls.[11]

Regarding PCO in our study, out of 114, 77 females in which 62(80.5%) had PCOs. Study published by Wolters Kluwer showed 30% AN found in patients with PCO.[3]

Hypertension was seen in 27(23.7%) patients in our study that was more prevalent in adults (p=0.001) that is quite significant. Munise Daye[15] in his study showed 10.8% had an increase systolic blood pressure and 12.1% with Diastolic blood pressure which is lower blood pressure than we found in our study. Persistent high insulin level leads to developing HTN. Thus, there is an association between AN and HTN which is a clinical sign for suspicion of early cardiovascular alterations.[6]

Sorof et al found increased prevalence of HTN if BMI percentiles increase from normal weight (2%) to over weight (11%) and Steinberg, Daniels et al found that HTN is a high-risk factor for common conditions so it should be track from childhood to adulthood.[7]

CONCLUSION:

Acanthosis nigricans is a common major cosmetic skin concern and important pathological problem among obese in our population. In our study, benign and HAIR-AN were most frequent types which is associated with obesity, increased BMI, raised waist circumference and increased hypertension in adolescents and adult groups. Hence, it is suggested to screen all adolescents and adults with acanthosis nigricans for obesity, DM, hypertension, PCO's, autoimmune conditions and IR regardless of age or gender. This may lead to identification of systemic disorders in dermatologically presenting acanthosis nigricans. Here, we may conclude that the early diagnosis of acanthosis in obese cases may improve quality of life of patients, prevent systemic complications and improved outcome.

Authors Contribution:
Furquana Niaz: Contributed to the conception, design, data collection, analysis and interpretation of data, Drafted the article and revising it critically for important intellectual content, final approval of the version to be published, submitted in the journal
Nadia Shams: Contributed to the conception, design, data collection, analysis and interpretation of data, Drafted the article and revising it critically for important intellectual content, final approval of the version to be published
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