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Research Article

CLINICO-DEMOGRAPHIC STUDY OF PATIENTS WITH ACANTHOSIS NIGRICANS - A MENACE FOR CARDIO-VASCULAR DISEASE

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ABSTRACT

Objective: Acanthosis nigricans (AN) is characterized by dark, coarse, and thickened skin with a velvety texture, involving the neck, the axillae, and the flexor of large joints. A significant association between coronary heart disease and patients with AN was noticed. Objectives were to study the prevalence, clinico-demographic, and etiological profile of patients presenting with AN and to draw relations, if any, with cardiovascular disease (CVD).

Methods: It was an observational, descriptive, institution-based cross-sectional study and was conducted at the out-patient department of dermatology, venereology and leprosy of a tertiary care hospital in the eastern part of India. An attempt was made to detect the etiological factor of the disease by noting the temporal association between the disease and any systemic associations, with special attention to CVD.

Results: High body mass index (BMI) was seen in 71.9% of cases, systolic hypertension in 35.3%, diastolic hypertension in 43.9%, raised fasting blood sugar (FBS) in 30.2%, and raised postprandial (PP) sugar in 15.8% of patients. A significant relationship was seen between high BMI, raised cholesterol, triglycerides, and PP blood sugar and systolic and diastolic hypertension.

Conclusion: In AN, patients who have a high BMI have the highest chance of developing CVD, as well as hypercholesterolemia and hypertryglyceridemia. Raised FBS is noted as an additional factor for developing diastolic hypertension.

Keywords: *Acanthosis nigricans*, Metabolic syndrome, Risk factor, Coronary heart diseases.

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INTRODUCTION

Acanthosis nigricans (AN) is a fairly common skin pigmentary disorder that causes areas of dark, thick, velvety skin in body folds and creases to be symmetrically distributed. It typically affects the armpits, groin, and neck. Usually, it affects people with obesity and is rarely a sign of cancer in an internal organ, like the stomach or liver. More recently, Schwartz described eight types of AN: (1) benign; (2) obesity-associated; (3) syndromic; (4) malignant; (5) acral; (6) unilateral; (7) medication-induced; and (8) mixed-type when two varieties are present [1]. The diagnosis of AN is largely clinical, with histopathology needed only for confirmation. A large number of systemic disorders are associated with AN, so early recognition of these conditions is essential for the prevention of such disease and its progression. We had embarked on this study to evaluate in a group of AN patients the clinical and demographic features of AN and to find out its association with cardiovascular disease (CVD), the most common epidemic with prominent public health influence.

Aims and objectives

To study the clinico-demographic profile of patients presenting with AN and physico-chemical changes. At the same time, to draw relations, if any, with CVD.

METHODS

It was an observational, descriptive, institution-based cross-sectional study over a period of 18 months in a tertiary care hospital in the eastern part of India that catering a very large geographic area. All ages and patients of both sexes with AN were included in the study. Institutional Ethics Committee clearance (No. MC/KOL/IEC/NON-SPON/414/11-2014) was taken before starting the study.

The demographic profile was recorded. A thorough clinical examination of the patients regarding morphology and the distribution of the lesion was performed. Body mass index (BMI), blood pressure (BP), and routine blood investigations were done in an institutional laboratory. Analysis is done to detect temporal associations between the disease and physico-chemical parameters and any systemic associations, with special attention to CVD.

The Asian standards for anthropometric and biochemical criteria of metabolic syndrome were followed [2]. The criteria in that standard are as follows: Normal BMI: 18.0–22.9 kg/m^2, overweight: 23.0–24.9 kg/m^2, obesity: >25 kg/m^2. Dysglycemia: fasting blood glucose level ≥100 mg/dl, hypertension: systolic ≥130 mmHg/diastolic ≥85 mmHg; high triglycerides: ≥150 mg/dL; low-density lipoprotein (LDL): 129 mg/dL is near optimal; and above 130 mg/dL is high. Total cholesterol is normal when it is ≤200 mg/dL and high when >200 mg/dL. Fasting insulin is normal at <25 IU and high at ≥25 IU.

RESULTS AND ANALYSIS

A total of 139 patients with AN attended during the above-mentioned period, with an estimated prevalence of 0.831/1000 population. The demographic profile of the study population is given in Table 1, with an age range of 1 year to 60 years and a mean age of 22.12±11.53 years. BMI was raised in 15.82% of cases, systolic BP was raised in 35.25%,

diastolic BP was 44.60%, total cholesterol was 30.21%, triglycerides were 38.84%, fasing sugar was 30.2%, postprandial blood sugar (PPBS) was 15.8%, and fasting insulin was raised in 23.01% of cases.

Table 1: Demographic pattern of acanthosis nigricans patients

Demographic Variables	Total=139	p-value
Age (Years)		
Mean±SD	22.12±11.53	
Median	18.00	
Sex		
(M: F)	55:84	p=0.0176
Residence		
Urban: Rural	100:39	<0.0001
Income		
APL: BPL	119:20	<0.0001
Education		
Illiterate: literate	2:137	<0.0001
Religion		
Hindu: Muslim	106:33	<0.0001
Occupation		
Unemployed: Employed	105:34	<0.0001
Duration of disease		
Mean±SD (months)	31.37±34.05	
(Range 2–240 months)		
Duration of disease		
<24 months: >24 months	55:84	p=0.0176

APL: Above poverty line, BPL: Below poverty line

Table 2: Distribution of acanthosis nigricans in different body areas

Body Areas	Total 139 (%)
Neck	133 (96)
Axillae	67 (48)
Antecubital fossa	18 (12.9)
Knee	3 (2.16)
Palm	4 (2.88)
Sole	4 (2.88)
Hand	26 (18.70)
Feet	8 (5.76)
Inner thigh, Groin	13 (9.35)
Nasal mucosa	2 (1.44)
Eyelid	2 (1.44)
Postauricular	2 (1.44)

The neck was the most common site involved (96%), followed by the axillae (48%) (Table 2). The majority of patients had multiple sites of involvement.

A categorical analysis of different parameters in AN patients showed that with different site involvement, the duration of disease is highest when the neck is the only involved site, BMI is highest (35.35±4.95) when the neck and three sites are involved, and systolic and diastolic BP, total cholesterol, and triglycerides also followed the same trend. Fasting insulin is highest when the neck and two sites are involved. Hand is the site where both fasting and PPBS increased (Table 3).

Associations noted with AN are Dermatoses Papulosa Nigra (43.9%), Acne Vulgaris (43.2%), Androgenetic Alopecia (38.1%), Skin Tags (32.4%), and Hirsuitism (30.9%).

The biochemical parameters in AN patients were as shown in Table 3.

It was an observational, descriptive, cross-sectional study. Still, we wanted to draw a correlation between AN, different physical and biochemical parameters, and the chances of developing coronary heart disease (CHD) in the presence of systolic and diastolic hypertension. For that reason, we defined all AN patients according to changes in duration of disease, BMI, fasting insulin, fasting blood sugar (FBS), PPBS, total cholesterol, triglycerides, and LDL, and compared them with the presence of systolic and diastolic hypertension for relative risk (RR) (Table 4). We noticed a significant correlation (high RR) between total cholesterol, and triglyceride, weak correlation with LDL, and very high correlation with high BMI – very high risk of developing systolic hypertension in Acanthosis Nigricas patients. The same trend was also noticed in patients with diastolic hypertension; here, FBS is an additional significant factor revealed.

We divided all patients into two groups: those who had normal systolic and diastolic pressure and those who had raised values. We compared both groups according to different physical and biochemical parameters like duration of disease, BMI, fasting insulin, FBS, PPBS, total cholesterol, triglycerides, and LDL and analyzed odds ratios (OR) (Table 5). BMI again came as a very high significant association, followed by raised cholesterol and triglycerides with systolic hypertension, and for diastolic hypertension raised PPBS came as an additional factor in addition to the other three.

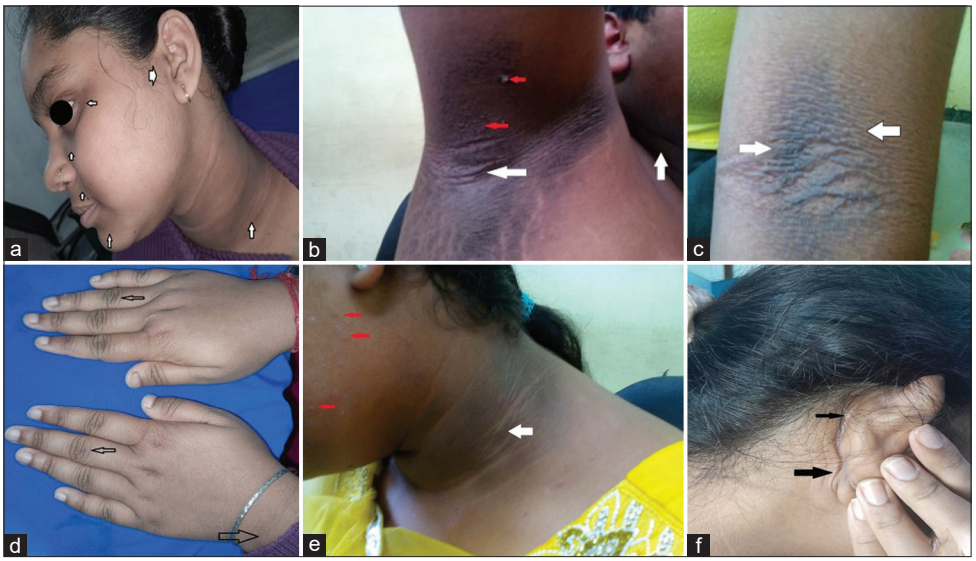

Fig. 1: Acanthosis nigricans (AN) in different sites (a) AN in multiple sites in a young girl- Neck, Periorbital, Perioral, anterior of ear, nasal fold. (b) AN of axillae, with skin tags (red arrow). Striae also present at same site. (c) Cubital fossa. (d) Over dorsum of small joint of fingers, also over wrist. (same pt of a), (e) AN on neck, acne on face (Red arrow), in adult female. (f) AN posterior of ear.

Table 3: Physical and biochemical parameters in acanthosis nigrican, in all cases and according to multiple site involvement

Parameters	Total n=139	Neck (44)	Neck+one site (37)	Neck+2 sites (29)	Neck+3 sites (6)	Hand (14)	Neck+Hand (9)
Duration of illness (Months)							
Mean±SD	31.37±34.05	42.36±51.12	27.49±20.94	24.07±18.70	18.00±12.00	28.14±27.34	31.11±19.26
Median	24	24	24.00	24.00	18	24	24.00
IQR	12–36	12–60	12–36	12.00–27.00	6.00–24.00	24.0–24.00	21.00–42.00
BMI							
Mean±SD	28.19±5.15	27.01±3.97	29.21±3.65	29.87±5.97	35.35±4.95	24.53±6.33	25.29±3.72
Median	28.50	27.29	29.16	29.41	37.00	22.19	23.46
IQR	24.03–31.11	23.89–30.11	27.34–31.22	25.05–34.16	29.22–38.82	20.34–26.83	22.76–27.80
Systolic BP							
Mean±SD	130.23±19.82	122.77±12.56	127.86±12.00	128.45±15.86	132.33±17.50	117.14±6.11	122.22±11.15
Median	130.00	120.00	128.00	130.00	141.00	120.00	120.00
IQR	110–148.00	113–130	119.50–138.00	120–140.50	110.00–140.00	110.00–120.00	113.50–128.00
Diastolic BP							
Mean±SD	81.46±8.93	80.14±8.60	80.05±9.50	84.10±10.97	88.00±14.42	76.14±4.99	82.44±6.77
Median	82.00	81	80.00	82.00	94.00	80.00	80.00
IQR	72.00–90.00	70–88	70.00–88.00	75.50–91.00	70.00–100.00	70.00–80.00	79.50–90.00
Fasting insulin							
Mean±SD	18.94±9.24	20.11±10.45	18.58±9.72	20.36±8.02	16.94±5.98	16.40±7.80	15.44±8.40
Median	19.17	18.84	19.00	21.30	20.15	15.68	16.03
IQR	11.57–24.03	12.12–28.41	10.68–22.64	12.19–24.50	11.90–21.07	11.69–19.70	7.77–21.89
Fasting Bl Sugar							
Mean±SD	96.92±21.37	98.25±24.97	94.46±12.97	96.34±18.63	89.00±5.69	104.71±37.80	95.56±5.00
Median	93.00	93.50	97.00	92.00	89.00	92.00	97.00
IQR	86.00–101	75.00–87.50	83.00–105.00	82.00–102.50	89.00–89.00	87.00–102.00	92.00–98.50
PPBS							
Mean±SD	122.57±25.93	124.13±30.43	125.46±18.51	118.86±25.33	95.17±16.40	135.21±29.28	113.67±15.32
Median	118	114.00	124.00	110.00	93.50	126.00	110.00
IQR	108–132	109.00–134.50	112.25±135.0	100.80–123.25	78.00–114.00	116.00–162.00	101.50–125.25
Total cholesterol							
Mean±SD	168.24±36.01	164.18±43.79	169.68±28.84	179.10±34.28	170.33±53.79	154.86±28.50	166.56±35.09
Median	162.00	154.5	177.00	173.00	156.00	155.00	169.00
IQR	145.00–189.50	122.9–139.5	148.00–185.50	153.25–203.00	128.00–182.00	142.00–176.00	142.00–185.75
Triglycerides							
Mean±SD	148.13±60.24	147.52±61.32	147.00±52.70	165.92±70.89	155.50±57.48	116.50±50.72	142.67±55.33
Median	139.00	130.00	142.00	145.00	160.50	107.00	123.00
IQR	102.50–192.00	99.50–186.00	110.00–165.75	125.50–211.25	120.00–201.00	69.00–151.00	95.75–201.25

IQL: Inter quartile range, BP: blood pressure, PPBS: Post prandial blood sugar

Table 4: Relative risk for development of systolic hypertension in patients who have changes in following category

Category	Systolic hypertension		Diastolic hypertension	
	Relative risk	p-value	Relative risk	p-value
BMI	6.9573	0.0492	10.2804	0.0177
FBS	1.2597	p=0.3100	1.3979	p=0.0762
PPBS	1.5000	p=0.1050	1.3512	p=0.1360
Fasting insuline	1.1748	p=0.5221	1.1889	p=0.4101
Total cholesterol	1.5735	p=0.0454	2.3220	p<0.0001
Triglyceride	1.7579	p=0.0113	2.1034	p=0.0001
Low density lipoprotein	1.6837	p=0.0561	1.7639	p=0.0038
Duration of disease	0.9821	p=0.9378	1.1102	p=0.5966
Acne	0.8778	p=0.5748	0.8185	p=0.3236

BMI: Body mass index, FBS: Fasting blood sugar, PPBS: Post prandial blood sugar

Table 5: Odds ratio between patients with systolic and diastolic hypertension and following category of associations

Category	Systolic hypertension		Diastolic hypertension	
	Odds ratio	p-value	Odds ratio	p-value
BMI	15.5294	p=0.0083	11.5988	p<0.0001
FBS	1.3813	p=0.3971	1.8795	p=0.0910
PPBS	1.8816	p=0.1712	5.8286	p=0.0007
Fasting insuline	1.3494	p=0.4692	1.3778	p=0.4278
Total cholesterol	2.2424	p=0.0494	7.0437	p<0.0001
Triglyceride	2.5031	p=0.0121	3.6519	p=0.0004
Low density lipoprotein	1.9535	p=0.2700	2.7925	p=0.1076
Duration of disease	0.9227	p=0.8243	1.0168	p=0.9619
Acne	0.9072	p=0.7886	0.5938	p=0.1363

BMI: Body mass index, FBS: Fasting blood sugar, PPBS: Post prandial blood sugar

We have noticed one patient with palm involvement and a short history who had internal malignancy and was treated accordingly in the concerned department.

DISCUSSION

In our study, patients with AN who came for other reasons were included. The mean age of this population was 22.12±11.53 years (Table 1), females outnumbered males (M: F 55:84), more are urban (100:39), affluent (APL: BPL 119:20), literate (2:137), unemployed (unemployed: employed 105:34), and religion Hinduism. These findings corroborate a similar study from western India, where the mean age was slightly higher (26.3±1.7 years) [3]. Though the lower-income group was affected more in that study [3], the educated higher-urban group was affected more in our study, which may be a sedentary habit with a higher calorie intake reason behind that.

The neck was the most common site, with 96% involvement, followed by the axillae (48%), the dorsum of the hand (18.7%), and the antecubital fossa (12.9%) (Table 2 and Fig. 1). Nearly the same pattern was noted in a study from western India, [3] where the neck (100%), axilla (80.6%), and groin (61.1%) were the predominantly affected sites. AN also occurred at the axillae (13.8%), the inframammary regions (10.3%), the nasal bridges, and periorally [3]. Acral AN appears over knee, ankle, phalangeal, and tarsophalangeal joints, usually more common in dark-complexioned individuals [4]. Our study supports that finding.

The pathophysiology of AN is a multifactorial stimulation of the proliferation of epidermal keratinocytes and dermal fibroblasts [5]. Insulin and insulin-like growth factor are suggested as promoters of this proliferation. Other proposed mediators include fibroblast growth factor receptors and tyrosine kinase receptors like epidermal growth factor receptors. All these receptors are present on keratinocytes and fibroblasts and stimulate growth [6].

Metabolic syndrome is defined as a group of disorders that includes, in addition to obesity, insulin resistance, dyslipidemia, arterial hypertension, and other metabolic disorders associated with CVD [6,7]. Metabolic Syndrome is nothing but the sum of different factors. These individual factors pose cardiovascular risks. Although the classification of metabolic syndrome is controversial, cardio-metabolic risk factors have been known to exist since pediatric age [7-10].

AN is one of the most common cutaneous manifestations of obesity and hyperinsulinism.

We have classified our patients according to the site of involvement. Single area of neck involved in 31.61%, neck and one more site in 26.61%, neck and two more sites in 20.86%, neck and three more sites in 4.31%, only dorsum of hand in 10.07%, and neck and hand combined in 6.47%.

We noticed that the duration of disease was highest in the neck group (42.36±51.12 months). Neck and three more sites had the highest BMI (35.35±4.95), systolic BP (132.33±17.50 mmHg), diastolic BP (84.10±10.97 mmHg), fasting insulin (20.36±8.02 mIU/L), total cholesterol (179.10±34.28 mg/dL), and triglycerides (165.92±70.89 mg/dL), though fasting and PPBS were highest in patients with involvement of dorsum of hand only (Table 3). We don't know the significance, but it may be that more area involvement is an indicator of more systemic involvement, which may lead to the early development of metabolic syndrome. This can only be inferred from a large prospective study.

CVD is the current age pandemic, and the concept of CVD risk factors is an integral part of modern medicine. These guided to develop effective treatment and preventive strategies for CVD in clinical practice. The Framingham study [11] was a breakthrough in our understanding of CVDs and identification of their major risk factors and related factors, which are high BP, high blood cholesterol, blood triglyceride, and high-density lipoprotein cholesterol (HDL-C) levels, age, gender, smoking, obesity, diabetes, physical inactivity and psychosocial issues. There is no single risk factor responsible for causing CVD; rather, multiple interrelated factors seem responsible for its development. The Framingham study provided information on Caucasian people, but other studies have shown that the major risk factors identified in this group apply universally to other racial and ethnic groups [12].

There is a well-documented association between obesity (BMI >30 kg/m^2) and hypertension. Further, cross-sectional studies indicate a direct linear correlation between body weight (or BMI) and BP. Centrally located body fat is a more important determinant of BP elevation than peripheral body fat. In longitudinal studies, a direct correlation exists between changes in weight and changes in BP over time. Sixty percent of hypertensive adults are >20% overweight. It has been established that 60–70% of hypertension in adults may be directly attributable to adiposity [13].

In our study, we noticed a significant correlation (high RR) between total cholesterol, and triglyceride, weak correlation with LDL, and very high correlation with high BMI – very high risk of developing systolic hypertension in Acanthosis Nigricas patients. The same trend was also noticed in patients with diastolic hypertensions; here, FBS is an additional significant factor revealed.

We compared both groups of patients who had normal systolic and diastolic pressure and who had raised values according to different physical and biochemical parameters like duration of disease, BMI, fasting insulin, FBS, PPBS, total cholesterol, triglycerides, and LDL, and analyzed OR for that. BMI again came as a very high significant association, followed by raised cholesterol and triglycerides with systolic hypertension, and for diastolic hypertension, raised PPBS came as an additional factor.

Our aim was to look for way for early detection and protection from developing CVD. The American College of Cardiology (ACC) and American Heart Association (AHA) have translated scientific evidence into clinical practice guidelines for the procedures of detection, management, or prevention of CVD. The ACC and AHA released updated risk-assessment guidelines in November 2013 for atherosclerotic CVD (ASCVD), where the changes and recommendations are as follows [12].

- A stroke is added to the list of coronary events traditionally covered by risk prediction equations
- The guidelines focus primarily on the 10-year risk of atherosclerosis-related events; they focus secondarily on the assessment of lifetime risk for adults aged 59 or younger without high shorter-term risk
- The strongest predictors of 10-year risk are identified as age, sex, race, total cholesterol, HDL-C, BP, BP treatment status, diabetes, and current smoking status
- Adjunct formulas for refining risk estimates by gender and race are provided
- If risk prediction needs to be further sharpened after risk prediction equations have been performed, the guidelines indicate that coronary-artery calcium scores, family history, high-sensitivity C-reactive protein, and the ankle-brachial index can be used.

The guidelines recommend that statin therapy be considered for individuals whose 10-year ASCVD event risk is 7.5% or greater.

Our effort was to strengthen the relationships between those risk factors in CHD, but a larger epidemiologic study is important before drawing inferences about all these factors.

CONCLUSION

Hence, we can conclude that (i) the neck is the mot common site, (ii) acne is the commonest association, (iii) multiple site involvement increases the chance of raised BMI, systolic and diastolic BP, total cholesterol, and triglycerides, and (iv) AN patients who have a high BMI have the highest chance of developing CHD, as well as hypercholesterolemia

and hypertryglyceridemia. Raised FBS is noted as an additional factor for developing diastolic hypertension. So, we can draw the inference that high BMI, hypercholesterolemia, hypertriglyceridemia, and raised fasting sugar are risk factors in AN patients for developing early CHD.

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AUTHORS CONTRIBUTION

Dr Suchibrata Das had contributed for planning of the study, analysis, manuscript writing and editing. Dr Arindam Sett was contributed for data collection, analysis, and manuscript writing. Manuscript finalized, edited, and submitted for publication by Dr Sangita Patra. Dr Abanti Saha was contributed planning of the study and editing. Prof Ramesh Chandra Gharami was overall monitored and mentor of the study, research reviewed and edited.

CONFLICTS OF INTERESTS

The authors affirm no conflicts of interest.

AUTHORS FUNDING

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