DOI: 10.7860/JCDR/2017/24902.10203

Original Article

Paediatrics Section

Prevalence of Acanthosis nigricans and Related Factors in Iranian Obese Children

FATEMEH SAYARIFARD[1], AZADEH SAYARIFARD[2], BAHAR ALLAHVERDI[3], SARA IPAKCHI[4], MASTANEH MOGHTADERI[5], BAHAREH YAGHMAEI[6]

ABSTRACT

Introduction: Recognition of Acanthosis nigricans (AN) provides important opportunities for screening of obesity syndrome, dyslipidemia, hypertension and insulin resistance with diabetes mellitus 2. Considering the high prevalence of obesity among Iranian children, we designed this study to estimate the prevalence of AN and related laboratory factors in Iranian obese children.

Materials and Methods: Seventy-one obese children were enrolled in this study. Diagnosis of AN was done by clinical examination. Body mass index (BMI), fasting blood sugar, total cholesterol, triglycerides (TG), alanine aminotransferase, aspartate aminotransferase (AST), alkaline phosphatase, high- and low-density lipoprotein cholesterol, insulin, thyroid-stimulating hormone, free thyroxin (fT4), calcium, phosphorus and 25-hydroxyvitamin D were measured with routine techniques. Collected data were compared between cases with AN and without AN. Independent t-test was used for comparison of variables.

Results: Twenty-five of children were female (35.2%). Forty-eight children (67.6%) had AN. In 20 cases (28.2%), homeostasis model assessment-insulin resistance (HOMA-IR) was <2.5 and in 51 (71.8%), HOMA-IR was more than 2.5. Mean BMI, insulin, HOMA-IR, TG and AST levels were significantly higher in cases with AN.

Conclusion: Obese children with AN are at risk of developing diabetes. Hence early identification of this feature and precise evaluation of children is recommended.

Keywords: BMI, Iran, Obesity, Pediatric

INTRODUCTION

Acanthosis nigricans (AN) is characterized by thickening and darkening of the skin, especially at the nape of neck, elbow, knee and knuckles [1-3]. AN is caused by factors that stimulate epidermal keratinocyte and dermal fibroblast proliferation. In the benign form of AN, the factor is insulin or an insulin-like growth factor (IGF) [4]. AN is most commonly associated with obesity. Obesity causes insulin resistance and hyperinsulinemia leads to obesity-related AN [5]. Relationship of AN with hyperinsulinemia has led to evaluations and precise follow-up of affected cases for type 2 diabetes [6-8].

The exact prevalence of AN is unknown. Some studies had reported the different prevalence of the AN in different regions of the world, for example, one study had reported 7% in unselected populations in Galveston, Texas, the United States and another study had reported 74% in obese people in Dallas, Texas, the United States [9,10]. The prevalence of AN in an urban population in Sri Lanka was reported 17.4% [11]. The prevalence of AN in New Mexico was 49.2% in obese adolescents compared with 7.7% in those who were not obese [12].

AN helps to identify individuals at high risk of developing the obesity syndrome, dyslipidemia, hypertension and insulin resistance with diabetes mellitus 2. Hence, recognition of AN provides important opportunities for health screening and prevention of diseases [13].

Considering the high prevalence of overweight (9.27%) and obesity (3.22%) among Iranian children [14-16] and few related studies to AN on Iranian children, we designed this study to estimate the prevalence of AN and related factors in Iranian obese children.

MATERIALS AND METHODS

This cross-sectional study was conducted in a children medical center (tertiary center affiliated by Tehran University of Medical Sciences), between August 2014 and March 2015.

For calculation of sample size with assuming, a prevalence of 49% of AN in obese children [12], d=0.12 (considering our time and financial restrictions), α=0.05 and a power of 0.80, sample size was calculated as 70.

All parents were asked to fill informed consent forms before the study. The study had been approved by Local Ethics Committee.

Inclusion criteria included Iranian children aged 4-13 years with body mass index (BMI) ≥95th percentile considering age and gender specific BMI.

Exclusion criteria included consumption of any medications that promote hyperinsulinemia and AN may appear as an adverse effect of them such as systemic glucocorticoids [17], systemic liver or kidney diseases and endocrine disorders such as diabetes, hypothyroidism, Cushing disease and history of cancer.

An expert pediatrician measured height and weight (each of them three times and then calculated the mean of each item). Using a tape measure in a standing position with bare feet and seca scales, weight and height were measured. Then, BMI (weight [kg]/height [m^2]) was calculated. Diagnosis of AN was done by visually examined each child's neck and axilla head and neck region, armpits, breasts, elbow, groin, knees and knuckles for the presence of AN by an expert pediatrician. AN was identified by the presence of dark, thick, velvety and pigmented skin in the region that was mentioned [12].

Fasting blood samples (5 cc) were collected after 12 h fasting and then centrifuged and stored in –20°C. fasting blood sugar, total cholesterol, triglycerides, Alanine Amino Transferase (ALT), Aspartate Amino Transferase (AST), Alkaline Phosphatase (ALP), High-Density Lipoprotein (HDL) Cholesterol and Low-Density Lipoprotein (LDL) cholesterol, insulin, thyroid-stimulating hormone and free thyroxin, calcium, phosphorus and 25-hydroxyvitamin D were measured with routine techniques. Collected data were compared between cases with and without AN.

All data were analyzed using SPSS software version 20 (SPSS Inc., Chicago, IL, USA). Data were presented as mean±SD for continuous or frequencies for categorical variables. Independent sample t-test was used for comparison of continuous variables. A p<0.05 were considered as significant.

RESULTS

Seventy-one children who were considered as obese were enrolled in this study. Twenty-five were female (35.2%). Mean age of children was 9.3±2 year and mean height and weight was 141.4±12.5 cm and 54±14.8 kg, respectively.

Forty-eight children had AN (67.6%). From who had AN, 33 (68.7%) children had only hyperpigmented thickening of skin over the nape of neck, 13 (27.1%) children had neck and axillae involvement and 2 (4.2%) had papillomatous formation with hyperpigmented thickening of skin neck and axillae skin.

Three children had hypertension (4.2%). [Table/Fig-1] shows basic characteristics and laboratory findings of all patients.

Thirteen cases (18.3%) had higher AST level and 7 (9.9%) had higher ALT level while ALP levels were in normal range in all cases. Sixty-four had normal calcium value while 7 (9.9%) had higher calcium values.

Forty-seven (66.2%) cases had vitamin D deficiency, 23 (32.4%) had vitamin D insufficiency and one case (1.4%) had vitamin D sufficiency.

In 20 cases (28.2%), homeostasis model assessment-insulin resistance (HOMA-IR) was <2.5 and in 51 (71.8%) HOMA-IR was more than 2.5.

Mean BMI, insulin, HOMA-IR, TG and AST levels were significantly higher in cases with AN [Table/Fig-1].

DISCUSSION

According to the results of this study, the prevalence of Iranian obese children was 67%. In a previous study which was conducted in China, frequency of AN was reported as 54% in Chinese obese children [18]. In another study conducted by Shalitin et al., AN was reported to be present in 56% of obese children in Israel [19]. Zambon et al. reported AN in 58% of overweight children and adolescents [20], while Mukhtar et al. reported prevalence of AN was 49.2% in adolescents with obesity in New Mexico [12].

Similar to Stuart et al. and Ng et al.'s findings in this study, the development of AN was not significantly different between male and female cases [9,18], which is also in agreement with Kluczynik et al.'s findings [21].

We also found that mean HOMA-IR, which is a simple, validated and practical marker of insulin resistance, was significantly higher in cases with AN. The frequency of values of HOMA-IR above the cutoff point (2.5) was significantly higher in AN group. HOMA-IR is a physiological estimate of glucose homeostasis, which is related with glycemic clamp in nondiabetic patients [22]. There is no consensus on the cutoff point value of HOMA-IR in children. In some studies, 2.5 is the accepted value and in others 4 is accepted cutoff point [23].

Identifying cases who are at risk of diabetes is important, as obesity and diabetes are increasing worldwide and adopting health programs in childhood will prevent occurrence of diabetes in adulthood.

Literatures show that presence of AN is associated with obesity, IR, type 2 diabetes and the metabolic syndrome [24,25]. It is considered that obesity alone is not a risk factor for AN development, while hyperinsulinemia by activating IGF-1 receptors leads to proliferation of the epidermis [26].

Mean values of BMI, TG and AST levels were significantly higher in cases with AN in our study, which is in agreement with Kluczynik et al.'s findings [21]. In their study, mean BMI was significantly different between AN and non-AN group, while mean SBD, DBP, triglyceride and HDL were not significantly different between two groups. Ng et al. investigated significantly higher values of BMI, HDL, TG, SBP and ALT in AN cases [18], while in this study, only mean values of TG and AST were significantly different between AN and non-AN groups.

High level of triglyceride and low level of HDL are characteristics of metabolic syndrome in children and adolescents [27]. On the other hand, high triglyceride levels and the IR index (HOMA-IR) are

Basic characteristics	Normal range	Mean±SD	Without acanthosis	With acanthosis	p value
Gender					
Male	-	25	6 (26.1%)	19 (39.6%)	0.2
Female	-	46	17 (73.9%)	29 (60.4%)	
BMI	BMI<85th percentile considering age and gender	26.4±3.5	24.6±3.1	27.3±3.3	0.002
FBS (mg/dl)	70-105	94±6	93.6±5.6	94.5±6.7	0.5
Insulin (uU/ml)	1.1-17	22.9±16.3	14.1±7.6	27.1±17.6	<0.001
HOMA-IR	<2.5	5.3±3.7	3.2±1.8	6.2±4	<0.001
HOMA-IR					
<2.5			12 (52.2%)	8 (16.7%)	0.002
>2.5			11 (47.8%)	40 (83.3%)	
TG (mg/dl)	35-135	143±69	116±44	156±76	0.006
Cholesterol (mg/dl)	Child: 120-200 Adult: 150-200	185±29	185±25	185±31	0.9
HDL (mg/dl)	>34	46±11	50.1±14	44.7±9.5	0.06
LDL (mg/dl)	Dessirbale: 13 Moderate risk: 130-159 High risk>160	109±26	105.6±20.1	111.1±29.1	0.4
AST (unit/L)	Up to 37	28±12	24±7	30.4±14.6	0.01
ALT (unit/L)	Up to 40	29±24	33.1±38	27.5±13.3	0.3
ALP (IU/L)	180-200	686±143	683.2±151	687±141	0.9
TSH	1-6 days: 0.7-15.2 2-20 weeks: 1.7-9.1 Adult: 0.3-5	2.7±1.1	2.7±1	2.8±1.1	0.6
fT4 (ng/dl)	0.8-2	9.5±1.6	9.8±1	9.4±1.8	0.2
Vitamin D	Less than 10 nM=deficiency, Between 10 and 29 nM=insufficiency, Between 30 and 100 nM=sufficient	11±6.5	9.8±4.6	11.6±7.3	0.2
Calcium (mg/dl)	8.6-10.3	9.7±0.45	9.7±0.3	9.8±0.4	0.6
Phosphorus (mg/dl)	>14 years: 2.7-4.5<14 years: 4.7-6.7	5±0.6	5.2±0.4	4.9±0.6	0.06
SBP	SBP<90th percentile considering age, gender and height	105	106±7	107±9	0.4
DBP	DBP<90th percentile considering age, gender and height	65	63±10	65±10	0.2

[Table/Fig-1]: Basic characteristics and laboratory findings of all patients.
Abbreviations: BMI: Body mass index, FBS: Fasting blood sugar, HOMA-IR: Homeostasis model assessment-insulin resistance, TG: Triglycerides, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, ALP: Alkaline phosphatase, TSH: Thyroid-stimulating hormone, fT4: Free thyroxin, SBP: Systolic blood pressure, DBP: Diastolic blood pressure. Significant P value is 0.05

considered as predisposing factors of intima-media thickness in children, which is used as a noninvasive measure of subclinical atherosclerosis [28].

We found that only AST level was significantly higher in AN cases and as a limitation of this study, we had no report of liver ultrasound.

Sartorio et al. claimed that ALT level is not an enough marker for NAFLD (Non-Alcoholic Fatty Liver Disease) diagnosis and its sensitivity for predicting NAFLD was 41% [29].

LIMITATION

Absence of findings of ultrasound is one of the limitations of this study. Other limitations include conduction of the study in a tertiary hospital and limited number of patients. Multicenter studies with larger sample sizes are recommended.

CONCLUSION

Obese children with AN are at risk of developing diabetes. Hence, identification of this symptom and precise evaluation of children with this symptom is recommended at early stage so that occurrence of disease can be prevented.

ACKNOWLEDGEMENTS

We are very thankful to all patients and coworkers for their assistance in this study.

REFERENCES

[1] Schwartz RA. Acanthosis nigricans. J Am Acad Dermatol. 1994;31(1):1-19.
[2] Stuart CA, Gilkison CR, Smith MM, Bosma AM, Keenan BS, Nagamani M. Acanthosis nigricans as a risk factor for non-insulin dependent diabetes mellitus. Clin Pediatr (Phila). 1998;37(2):73-9.
[3] Stuart CA, Driscoll MS, Lundquist KF, Gilkison CR, Shaheb S, Smith MM. Acanthosis nigricans. J Basic Clin Physiol Pharmacol. 1998;9:407-18.
[4] Fasunla JA, Ijaduola GT. Acanthosis nigricans in the head and neck region. Ann Ib Postgrad Med. 2008;6(1):53-6.
[5] Nguyen TT, Keil MF, Russell DL, Pathomvanich A, Uwaifo GI, Sebring NG, et al. Relation of acanthosis nigricans to hyperinsulinemia and insulin sensitivity in overweight African American and white children. J Pediatr. 2001;138(4):474-80.
[6] Kobaissi HA, Weigensberg MJ, Ball GD, Cruz ML, Shaibi GQ, Goran MI. Relation between acanthosis nigricans and insulin sensitivity in overweight Hispanic children at risk for Type 2 diabetes. Diabetes Care. 2004;27(6):1412-6.
[7] Litonjua P, Piñero-Piloña A, Aviles-Santa L, Raskin P. Prevalence of acanthosis nigricans in newly-diagnosed Type 2 diabetes. Endocr Pract. 2004;10(2):101-6.
[8] Stoddart ML, Blevins KS, Lee ET, Wang W, Blackett PR; Cherokee Diabetes Study. Association of acanthosis nigricans with hyperinsulinemia compared with other selected risk factors for Type 2 diabetes in Cherokee Indians: The Cherokee Diabetes Study. Diabetes Care. 2002;25(6):1009-14.
[9] Stuart CA, Pate CJ, Peters EJ. Prevalence of acanthosis nigricans in an unselected population. Am J Med. 1989;87(3):269-72.
[10] Hud JA Jr, Cohen JB, Wagner JM, Cruz PD Jr. Prevalence and significance of acanthosis nigricans in an adult obese population. Arch Dermatol. 1992;128(7):941-4.
[11] Dassanayake AS, Kasturiratne A, Niriella MA, Kalubovila U, Rajindrajith S, de Silva AP, et al. Prevalence of acanthosis nigricans in an urban population in Sri Lanka and its utility to detect metabolicsyndrome. BMC Res Notes. 2011;4:25.
[12] Mukhtar Q, Cleverley G, Voorhees RE, McGrath JW. Prevalence of acanthosis nigricans and its association with hyperinsulinemia in New Mexico adolescents. J Adolesc Health. 2001;28(5):372-6.
[13] Maitra SK, Payne CM. The obesity syndrome and acanthosis nigricans. Acanthosis nigricans is a common cosmetic problem providing epidemiological clues to the obesity syndrome, the insulin-resistance syndrome, the thrifty metabolism, dyslipidaemia, hypertension and diabetes mellitus Type II. J Cosmet Dermatol. 2004;3(4):202-10.
[14] Moayeri H, Rabbani A, Keihanidoust ZT, Bidad K, Anari S. Overweight adolescents: A group at risk for metabolic syndrome (Tehran adolescent obesity study). Arch Iran Med. 2008;11(1):10-5.
[15] Kelishadi R, Ardalan G, Gheiratmand R, Majdzadeh R, Hosseini M, Gouya MM, et al. Thinness, overweight and obesity in a national sample of Iranian children and adolescents: CASPIAN Study. Child Care Health Dev. 2008;34(1):44-54.
[16] Mirmohammadi SJ, Hafezi R, Mehrparvar AH, Rezaeian B, Akbari H. Prevalence of overweight and obesity among Iranian school children in different ethnicities. Iran J Pediatr. 2011;21(4):514-20.
[17] Puri N. A study of pathogenesis of acanthosis nigricans and its clinical implications. Indian J Dermatol. 2011;56(6):678-83.
[18] Ng HY, Young JH, Huen KF, Chan LT. Acanthosis nigricans in obese Chinese children. Hong Kong Med J. 2014;20(4):290-6.
[19] Shalitin S, Abrahami M, Lilos P, Phillip M. Insulin resistance and impaired glucose tolerance in obese children and adolescents referred to a tertiary-care center in Israel. Int J Obes (Lond). 2005;29(6):571-8.
[20] Zambon MP, Antonio M, Mendes RT, Filho AB. Características clínicas e laboratoriais de crianças e adolescentes obesos. Rev Paul Pediatr. 2007;25(1):27-32.
[21] Kluczynik CE, Mariz LS, Souza LC, Solano GB, Albuquerque FC, Medeiros CC. Acanthosis nigricans and insulin resistance in overweight children and adolescents. An Bras Dermatol. 2012;87(4):531-7.
[22] Singh B, Saxena A. Surrogate markers of insulin resistance: A review. World J Diabetes. 2010;1(2):36-47.
[23] Nsiah-Kumi PA, Beals J, Lasley S, Whiting M, Brushbreaker C, Erickson J, et al. Body mass index percentile more sensitive than acanthosis nigricans for screening native American children for diabetes risk. J Natl Med Assoc. 2010;102(10):944-9.
[24] Kong AS, Williams RL, Rhyne R, Urias-Sandoval V, Cardinali G, Weller NF, et al. Acanthosis Nigricans: High prevalence and association with diabetes in a practice-based research network consortium - A PRImary care multi-ethnic network (PRIME Net) study. J Am Board Fam Med. 2010;23(4):476-85.
[25] Drobac S, Brickman W, Smith T, Binns HJ. Evaluation of a Type 2 diabetes screening protocol in an urban pediatric clinic. Pediatrics. 2004;114(1):141-8.
[26] Lee JM, Okumura MJ, Davis MM, Herman WH, Gurney JG. Prevalence and determinants of insulin resistance among US adolescents a population-based study. Diabetes Care. 2006;29(11):2427-32.
[27] Reinehr T, de Sousa G, Toschke AM, Andler W. Comparison of metabolic syndrome prevalence using eight different definitions: A critical approach. Arch Dis Child. 2007;92(12):1067-72.
[28] Fang J, Zhang JP, Luo CX, Yu XM, Lv LQ. Carotid Intima-media thickness in childhood and adolescent obesity relations to abdominal obesity, high triglyceride level and insulin resistance. Int J Med Sci. 2010;7(5):278-83.
[29] Sartorio A, Del Col A, Agosti F, Mazzilli G, Bellentani S, Tiribelli C, et al. Predictors of non-alcoholic fatty liver disease in obese children. Eur J Clin Nutr. 2007;61(7):877-83.

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Pediatric Endocrinologist, Growth and Development Research Center, Children's Medical Center, Pediatrics Center of Excellence, Tehran University of Medical Sciences, Tehran, Iran.
2. Assistant Professor, Community Medicine Specialist, Growth and Development Research Center, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran.
3. Assistant Professor, Pediatric Gastroenterologist, Research Center for Pediatric Gastroenterology and Hepatology, Children's Medical Center, Pediatrics Center of Excellence, Tehran University of Medical Sciences, Tehran, Iran.
4. Medical doctor, Department of Paediatric, Tehran University of Medical Sciences, Tehran, Iran.
5. Pediatric Nephrologist, Chronic Kidney Disease Research Center, Children's Medical Center, Pediatrics Center of Excellence, Tehran University of Medical Sciences, Tehran, Iran.
6. Assistant Professor, Pediatric Intensifier, Children's Medical Center, Pediatrics Center of Excellence, Tehran University of Medical Sciences, Tehran, Iran.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Bahar Allahverdi,
Qarib St, Keshavarz Blvd, Tehran 1419733151, Iran.
E-mail: bahar_allahverdi@yahoo.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Oct 19, 2016**
Date of Peer Review: **Dec 22, 2016**
Date of Acceptance: **Apr 11, 2017**
Date of Publishing: **Jul 01, 2017**