Acanthosis Nigricans Identifies Youth at High Risk for Metabolic Abnormalities

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Objective To determine the prevalence of abnormal glucose homeostasis and cardiovascular risk factors in youth with acanthosis nigricans (AN).

Study design Youth (8-14 years) were recruited from community pediatric offices. Each subject underwent a questionnaire, a targeted physical examination, and an oral glucose tolerance test.

Results Subjects (n = 236) with AN of the neck (AN+) (60% Hispanic, 30% African American, 54% female, body mass index [BMI] z-score 2.3 kg/m^2) and 51 youth without AN (65% Hispanic, 22% African American, 37% female, BMI z-score 2.1 kg/m^2) completed the study. Twenty-nine percent of the AN+ group had abnormal glucose homeostasis, 27% had systolic blood pressure > 95th percentile, and 50% had high-density lipoprotein–cholesterol ≤5th percentile. Once corrected for sex, puberty, maternal education, and BMI z-score, AN remained significantly associated with insulin resistance and abnormal glucose homeostasis. For youth in the AN+ group, homeostasis model assessment of insulin resistance, female sex, and positive glutamic acid decarboxylase antibodies remained significantly and independently associated with impaired glucose tolerance.

Conclusions Youth in the AN+ group had severe insulin resistance, and more than 1 in 4 already had abnormal glucose homeostasis. AN identified a high-risk population, for whom appropriate interventions have the potential to attenuate or even prevent the development of diabetes and further metabolic abnormalities. *(J Pediatr 2010;156:87-92)*.

Type 2 diabetes mellitus is becoming increasingly prevalent in adolescents.[1] Adolescents appear to have similar risk factors as adults for development of type 2 diabetes: obesity, high-risk racial/ethnic backgrounds (ie, Latino), family history of diabetes, and evidence of insulin resistance.[2] In addition the youth with type 2 diabetes have been found to have high-risk cardiovascular profiles with reports of hypertension and atherogenic lipid profiles.[3]

Although there is increasing attention to type 2 diabetes in adolescents in the media and increased reporting of type 2 diabetes in this age group, the prevalence of type 2 diabetes remains relatively low. Goran et al[4] have examined Hispanic youth with a family history of diabetes, finding a prevalence of impaired glucose tolerance (IGT) of 28%. Similarly, 25% of severely obese youth studied by Caprio et al[5] had IGT.

Acanthosis nigricans (AN) is a physical sign associated with obesity and insulin resistance that has been found in up to 90% of the youth with type 2 diabetes mellitus.[6] Yet not all youth with AN development diabetes. We previously reported AN in approximately 1 of 5 African American and Hispanic youth, with increasing prevalence as the body mass index (BMI) z-score increases.[7] Given the prevalence of AN, its easy recognition (although its visible absence does not rule out AN) and its association with obesity and insulin resistance, we decided to use AN to identify a population of youth possibly enriched with insulin resistance to further study the pathophysiological condition of abnormal glucose homeostasis.

Methods

This study was approved by the institutional review boards at Children's Memorial Hospital and Northwestern University. Patients were recruited from primary pediatric offices in the Chicago region (primarily urban). Information regarding the study was given to families who then contacted us to set up a screening visit to verify inclusion criteria: 8 to 14 years of age, no steroid medication for the previous month (inhaled, oral, or topical), and no chronic disease associated with autoimmune disease. Subjects with a neck score of at least 2 according to Hale et al[8] were categorized in the AN+ group. Youth without AN

AN	Acanthosis nigricans	HOMA-IR	Homeostasis model assessment of insulin resistance
AN+	With acanthosis nigricans		
AN–	Without acanthosis nigricans	IFG	Impaired fasting glucose
BMI	Body mass index	IGT	Impaired glucose tolerance
DM	Diabetes mellitus	PCOS	Polycystic ovary syndrome
GAD	Glutamic acid decarboxylase	$S_{i,}$	Insulin sensitivity
HDL	High-density lipoprotein		

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(AN–) of the neck and a BMI z-score >85th percentile were also recruited for the reference population. Parental consent and child assent for youth ≥12 years of age was obtained.

In preparation for visit 1 at the outpatient General Clinical Research Center, subjects were told to have a carbohydrate-rich diet for the 3 days before and not to eat for 8 hours before visit. Anthropometric measurements were performed, blood pressure was taken 3 times, 5 minutes apart, the numbers were averaged, and an intravenous antecubital catheter was placed. Blood was drawn for laboratory studies at time –15 and –1 and 120 minutes. A glucose load (1.75 g/kg, max 75 g) was given at time 0 to be drunk within 5 minutes. A physician performed the examination for the AN score and Tanner staging, and a research assistant gathered demographic, socioeconomic, family history, and medical information.

Definitions

Blood pressure was categorized according to age, sex, and height.[9] Lipids were categorized according to age and sex norms.[10] Glucose abnormalities were defined according to criteria from the American Diabetes Association.[11,12] *Abnormal glucose homeostasis* refers to any combination of impaired fasting glucose (IFG), IGT, or diabetes (DM) on the basis of fasting or stimulated results. When evaluating factors associated with IGT in youth in the AN+ and AN– groups, youth with IFG only were excluded, increasing the uniformity of the study population, and those with DM were grouped with those with IGT. The AN neck score of 2 or 3 was mild, and 4 was severe. Other definitions included low high-density lipoprotein (HDL ≤ 5th percentile); elevated triglycerides, total cholesterol, systolic blood pressure, and diastolic blood pressure (≥ 95th percentile); elevated glutamic acid decarboxylase (GAD) antibodies (GAD index > 0.085). Subjects were classified as having possible polycystic ovary syndrome (PCOS), if they had at least 1 of the following criteria: hirsutism (Ferriman Gallwey score ≥ 8), moderate to severe acne, elevated androgens (elevated testosterone ≥ 1.98 nmol/L [57 ng/dL], bioavailable testosterone ≥ 0.62 nmol/L [18 ng/dL]), as well as irregular menses (≥ 6 weeks between menses after 18 months postmenarcheor, ≥14 years of age and no menses).

Glucose was assayed by enzymatic method, initially by YSI glucose oxidase and then glucose hexokinase. Insulin was assayed by radioimmunoassay with Linco kits (Linco Research, St. Charles, Missouri; intra CV 3.2%, inter CV 3.9%, recovery 96%, cross-reactivity with human proinsulin < 0.2%). Total cholesterol, HDL-cholesterol, and triglycerides were determined with the Beckman Synchron LX20 system (Beckman Coulter, Fullerton, California). Hemoglobin A1c was assayed using affinity chromatography HPLC. GAD65 autoantibody index was performed at Northwest Lipid Research Laboratories with a radioimmunoprecipitation assay as described previously.[13] Total testosterone by solid-phase radioimmunoassay and bioavailable testosterone using ^{3}H-testosterone exchange equilibrium assay, both performed at Penn State University after dilution.

Statistical Analysis

Demographic, clinical, and metabolic characteristics were compared with the *t* test or Mann-Whitney for continuous variables and the χ^2 test or Fisher exact test for categorical variables. Univariate and multiple linear/ logistic regression were used to examine the relationship between the continuous/binary outcome of interest and the potential risk factors. The paired *t*-test, Wilcoxon signed ranks test, and the McNemar test were used, as appropriate, to compare differences in an analysis of 48 youth in the AN+ group matched with 48 youth in the AN– group (criteria – ethnicity at least 1 parent of same ethnicity, BMI z-score ± 0.2 kg/m^2, sex the same, Tanner stage ± 1 stage). Three youth in the AN– group could not be matched to youth in the AN+ group and were therefore excluded from the paired analysis. Fasting and 120-minute insulin concentrations, as well as homeostasis model assessment of insulin resistance (HOMA-IR) were transformed by use of the natural log to obtain normally distributed data. Significance was defined at the $P < .05$ level. Univariate and multivariate analysis were performed with SAS software version 9.1 (SAS Institute, Cary, North Carolina). Some univariate analysis was performed with SPSS software version 12 (SPSS, Chicago, Illinois).

Results

Three hundred six youth between 8 and 14 years of age completed the study. When there were 2 or more siblings with or without AN, only 1 sibling was randomly chosen to be included in the analysis, leaving 287 subjects: 236 subjects in the AN+ group and 51 subjects in the AN– group.

Subject characteristics, physical findings, and laboratory results are found in Table I. Most families (1) identified themselves as Latino or African American; (2) had a mother who reached the equivalent of a high school education or lower; (3) had limited financial resources; and (4) had a parent or grandparent with diabetes (Table I). On physical examination, the 287 subjects were primarily obese (1 subject in the AN+ group had a normal BMI, 9 subjects in the AN+ group, and 5 in the AN– group had a BMI >85th percentile but < 95th percentile).

Of the youth in the AN+ group, approximately 6% had IFG alone, 14% IGT alone, 6% IFG and IGT, and 2% had diabetes. The 4 subjects classified as having diabetes met diagnostic criteria atypically: 2 subjects had fasting blood glucose ≥ 7.0 mmol/L (126 mg/dL), but impaired glucose tolerance and 2 had a 2-hour stimulated glucose ≥ 11.1 mmol/L (200 mg/dL) with normal fasting glucoses of 5.2 and 5.5 mmol/L (93 and 99 mg/dL). Of the youth in the AN– group, 2% had IFG, 4% IGT, 6% IFG and IGT, and nobody fit criteria for diabetes.

As shown in Table I, the subjects in the AN+ group were significantly more likely to be females, have lower maternal education, be in later stages of puberty, and have higher BMI z-scores. On the basis of univariate analysis, the subjects

Table I. All youth: subjects AN+ vs subjects AN–

	AN+ (n = 236)	AN– (n = 51)	*P* value	*P* value adjusted*
Descriptives				
Age, yrs	11.7 ± 1.8	11.3 ± 2.0	.141	.658
Female sex	54%	37%	.028	N/A
Ethnicity (Hisp, AA, other)	60%, 30%, 10%	65%, 22%, 14%	.398	.865
Reported family income (≥$40 000)†	18%	28%	.091	.173
Maternal education (>GED)‡	35%	58%	.003	N/A
Maternal gestational diabetes§	12%	15%	.599	.214
History of DM in parent or grandparent	70%	69%	.903	.144
Physical examination				
BMI z-score	2.3 ± 0.4	2.1 ± 0.3	<.001	N/A
SBP ≥ 95th percentile‖	27%	14%	.041	.296
Tanner stage: prepubertal¶	18%	41%	<.001	N/A
AN: Severe of the neck	64%	N/A	N/A	N/A
Laboratory findings				
Fasting glucose (mmol/L)	5.2 ± 0.4	5.1 ± 0.4	.22	.77
Fasting insulin (pmol/L)	234 ± 138	126 ± 54	<.001	<.001
120 minute glucose (mmol/L)	6.9 ± 1.3	6.4 ± 1.1	.013	.0587
120 minutes insulin (pmol/L)	1260 ± 1098	642 ± 534	<.001	<.001
Abnormal glucose homeostasis	29%	12%	.012	.0437
HgbA1c#	5.5% ± 0.3%	5.3% ± 0.5%	.001	.0741
Elevated GAD antibody**	10%	4%	.189	.1403
Triglycerides ≥ 95th percentile	16%	8%	.188	.287
HDL ≤ 5th percentile	50%	35%	.05	.091
HOMA-IR	9.0 ± 6.0	4.7 ± 2.2	<.001	<.001

Hisp, Hispanic; *AA,* African American; *GED,* general equivalency diploma; *SBP,* systolic blood pressure.
**P* value after correction for BMI z-score, Tanner stage, sex, and maternal education; continuous variables (mean ± SD).
†N = 228 vs 50.
‡N = 235 vs 50.
§N = 228 vs 48.
‖N = 234 vs 51.
¶N = 233 vs 51.
#N = 232 vs 51.
**N = 235 vs 51.

in the AN+ group had significantly higher systolic blood pressure, higher 2-hour glucose, more glucose abnormalities, higher markers of insulin resistance, and lower HDL-cholesterol. After adjusting for sex, maternal education, pubertal status, and BMI z-score, AN positivity remained significantly associated with higher stimulated 2-hour glucose concentrations, abnormal glucose homeostasis, and higher markers of insulin resistance. Results were similar when AN neck severity was considered instead of the presence or absence of AN, with the addition of 2 significant positive associations: severity of AN with (1) high fasting glucose ($P = .048$) and (2) low HDL-cholesterol ($P = .016$) (Data not shown in table).

A second approach to exploring the importance of AN used a matched pairing of youth in the AN+ group to youth in the AN– group. As above, AN positivity was significantly associated with higher stimulated 2-hour glucose concentrations and higher markers of insulin resistance (data not shown). In the matched analysis, youth in the AN+ group again were more likely to have abnormal glucose tolerance (25% vs 10%), but the difference was not statistically significant.

Table II displays the subject characteristics, clinical findings, and laboratory data of youth in the AN+ and AN– groups according to their glucose tolerance status. Further analysis examined risk factors associated with presence of impaired glucose tolerance in youth in the AN+ and AN– groups separately. Youth in the AN+ group with IGT were significantly more likely to be Hispanic and female and to have severe AN but were not heavier and had only slightly stronger family histories of diabetes that were not statistically significant. HOMA-IR was almost doubled in youth with IGT compared with those with NGT, suggesting youth with IGT were significantly more insulin resistant. Although youth in the AN+ group with IGT were more likely to have hypertriglyceridemia, they were not more likely to have abnormal HDL-cholesterol.

Variables that were of clinical relevance and significant at 0.1 level in the univariate analysis were considered for the multivariate analysis. We used the stepwise selection procedure to build the final model and explored the interactions between the significant main effects. As a result, the final model included HOMA-IR ($P < .001$), GAD antibody positivity ($P = .001$), sex ($P < .001$), and the interaction of GAD positivity and sex ($P = .025$). The odds of IGT increased by 1.2 times (95% confidence interval 1.1-1.3) with every unit increase in HOMA-IR, when sex and GAD positivity were fixed.

Youth in the AN– group with IGT were more likely to be Hispanic, weighed less, had stronger family histories of diabetes, and were male, but neither of these differences reached statistical significance (Table II). Elevated HOMA-IR was associated with IGT in subjects in the AN– group as it had been with subjects in the AN+ group. Multivariate analysis was not performed because of small sample size.

Table II. NGT vs IGT by presence of acanthosis nigricans (subjects with IFG only excluded)

	With Acanthosis			No Acanthosis		
	NGT (n = 168)	IGT (n = 53)	*P* value	NGT (n = 45)	IGT (n = 5)	*P* value
Descriptives						
Age, yrs	11.7 ± 1.8	11.8 ± 1.7	.792	11.3 ± 2.1	10.6 ± 1.6	.488
Ethnicity (Hisp, AA, other)	58%, 34%, 8%	64%, 19%, 17%	.045	62%, 22%, 16%	100%, 0%, 0%	.376
Female sex	48%	77%	<.001	42%	0%	.142
Reported family income (≥$40 000)*	15%	26%	.098	29.5%	20%	1
Maternal education (>GED)†	38%	32%	.456	57%	80%	.636
Maternal gestational diabetes‡	11%	14%	.57	12%	40%	.154
History of DM in parent or grandparent	69%	76%	.33	64%	100%	.16
Physical examination						
BMI z score	2.3 ± 0.4	2.3 ± 0.4	.248	2.1 ± 0.3	2.0 ± 0.5	.398
SBP ≥ 95th percentile§	27%	29%	.713	16%	0	
Tanner stage: prepubertal‖	19%	11%	.178	42%	40%	1
AN neck score severe	60%	77%	.022	0%	0%	
Laboratory findings						
Fasting glucose (mmol/L)	5.0 ± 0.3	5.4 ± 0.6	<.001	4.9 ± 0.3	5.7 ± 0.7	.007
Fasting insulin (pmol/L)	198. ± 102	318 ± 192	<.001	120 ± 42	186 ± 96	.036
120-minute glucose (mmol/L)	6.3 ± 0.8	8.9 ± 1.1	<.001	6.2 ± 0.8	8.4 ± 0.9	<.001
120-minute insulin (pmol/L)	930 ± 702	2310 ± 1488	<.001	558 ± 426	1332 ± 930	.007
HgbA1c¶	5.4% ± 0.3%	5.5% ± 0.3%	.013	5.2% ± 0.5%	5.5% ± 0.5%	.449
Elevated GAD antibody	8%	19%	.022	4%	0%	1
Triglycerides ≥ 95th percentile	12%	25%	.025	7%	20%	.353
HDL ≤ 5th percentile	51%	45%	.5	36%	20%	.65
HOMA-IR	7.4 ± 3.9	13.1 ± 8.7	<.001	4.3 ± 1.6	7.6 ± 3.9	.009

Hisp, Hispanic; *AA,* African American; *GED,* general equivalency diploma; *SBP,* systolic blood pressure.
Continuous variables (mean ± SD).
*163 vs 51: 44 vs 5.
†167 vs 53: 44 vs 5.
‡163 vs 50: 42 vs 5.
§168 vs 51.
‖165 vs 53.
¶166 vs 51.

Given the preponderance of abnormal glucose homeostasis in females in our study population, we more closely explored the subject characteristics, clinical findings, and laboratory data of our youth in the AN+ group according to sex (Table III). Among the youth in the AN+ group, females and males had similar study characteristics (age, income, education, family histories of DM), except that a higher percentage of males were of Hispanic origin. In terms of physical attributes, the females had significantly lower BMI z-scores and were more often pubertal. All 4 youth with previously undiagnosed diabetes were female. As shown in Table III, females had significantly higher markers of insulin resistance. Dyslipidemia (elevated triglycerides ≥95th percentile and decreased HDL-cholesterol ≤5th percentile), however, was more prevalent among the males.

Of the 128 females in the AN+ group, 30% were hirsute, and 17% had abnormal total or bioavailable testosterone. Sixty-eight (53%) girls had menarche. Of these 68 girls, 42% were hirsute, 52% had acne, 31% had elevated androgens, and 72% had either clinical or biochemical evidence of hyperandrogenemia. Twenty-one percent fit the definition of PCOS with evidence of hyperandrogenemia and oligomenorrhea. For the females with menarche, no significant associations were found between the presence of PCOS or its individual features and abnormal glucose homeostasis. In addition, total and bioavailable testosterone significantly correlated with HOMA-IR with Spearman coefficients of 0.350 ($P = .003$) and 0.438 ($P < .001$), respectively.

Discussion

We identified 4 individuals with previously undiagnosed diabetes, 2 of whom would have not been identified as having abnormal glucose homeostasis if screened by a fasting glucose. This is especially concerning because a fasting glucose is (1) often the chosen method for screening for type 2 diabetes by practitioners because of its practicality and (2) the preferred test for screening for type 2 diabetes according to the American Diabetes Association.[12] In our research sample, the prevalence of IFG or IGT of 29% is comparable with findings from other high-risk populations: 28% in overweight Latino children with a family history of type 2 diabetes[4]; 25% in youth with BMI >95th percentile.[5]

Interestingly, in this obese population, BMI z-score was not significantly associated with abnormal glucose homeostasis, suggesting other factors such as truncal or body fat, may make significant independent contributions to IFG or IGT. In addition, family history and gestational diabetes, both known risk factors for the development of type 2 diabetes, were not associated with abnormal glucose homeostasis. Perhaps the high prevalence of family history in youth in the AN+ and AN– groups, with and without IGT, made it difficult to detect significant differences.

In addition to insulin resistance, multivariate analysis showed females to be at significantly increased risk of abnormal glucose homeostasis, which is consistent with the

Table III. Male vs female: all subjects AN+ only

	Males (n = 108)	Females (n = 128)	*P* value
Descriptives			
Age, y	11.6 ± 1.8	11.8 ± 1.8	.321
Ethnicity (Hisp, AA, other)	68%, 27%, 6%	54%, 33%, 13%	.047
Reported family income (≥$40 000)*	17%	18%	.932
Maternal education (>GED)†	35%	36%	.828
Maternal gestational diabetes‡	12%	12%	.897
History of DM in parent or grandparent	68%	71%	.561
Physical examination			
BMI z score	2.4 ± 0.3	2.2 ± 0.4	<.001
SBP ≥ 95th percentile§	30%	25%	.42
Tanner stage: prepubertal‖	31%	7%	<.001
AN neck score severe	63%	66%	.67
Laboratory findings			
Fasting glucose (mmol/L)	5.1 ± 0.4	5.1 ± 0.5	.601
Fasting insulin (pmol/L)	216 ± 126	246 ± 150	.025
120-minute glucose (mmol/L)	6.7 ± 1.1	7.1 ± 1.5	.156
120-minute insulin (pmol/L)	1050 ± 870	1440 ± 1230	.004
Abnormal glucose tolerance	19%	37%	.004
HgbA1c¶	5.5% ± 0.3%	5.4% ± 0.3%	.13
Elevated GAD antibody	8%	12%	.38
Triglycerides ≥ 95th percentile	19%	14%	.353
HDL ≤ 5th percentile	60%	42%	.006
HOMA-IR	8.3 ± 5.3	9.6 ± 6.4	.043

Hisp, Hispanic; *AA,* African American; *GED,* general equivalency diploma; *SBP,* systolic blood pressure.
Continuous variables (mean ± SD).
*104 vs 124.
†107 vs 128.
‡104 vs 124.
§107 vs 127.
‖106 vs 127.
¶106 vs 126.

increased prevalence of type 2 diabetes in females compared with males.[2] Adolescents with PCOS are known to be at high risk for abnormalities of carbohydrate metabolism.[13,14] In our study, however, the menarchal females in the AN+ group with features of PCOS were not statistically more likely to have abnormal glucose homeostasis. This finding suggests that other factors may be contributing to the increase in abnormalities in carbohydrate metabolism seen in our females in the AN+ group. Yet we did find a concerning number of our menarchal females in the AN+ group to be at high risk for PCOS. Almost 1 in 5 females with menarche fit our definition for PCOS, and almost 1 in 3 had elevated androgens.

Multivariate analysis also showed that GAD autoimmunity was associated with increased risk of abnormal glucose homeostasis. Further research will be needed to explain this finding. The presence of GAD antibodies in a clinical scenario consistent with type 2 diabetes has been established.[15-17] Tfayli et al[17] found defects in beta cell function in obese youth diagnosed with type 2 diabetes who were antibody positive. Further research will need to delineate the role GAD autoimmunity will have in the progression of abnormal glucose homeostasis to the development of diabetes in these youth.

Our data also suggested that AN conferred risk of insulin resistance beyond that conferred by adiposity alone. Mukhtar et al[18] found similar findings in 12- to 15-year-old youth from New Mexico middle school students, although they used obesity and AN as dichotomous variables and fasting insulin as a marker of insulin resistance. Goran et al[19] investigated the relationship between insulin sensitivity (S_i) and AN in Hispanic 8- to 12-year-old youth with a family history of type 2 diabetes. Unlike our study they measured insulin sensitivity directly from a frequently sampled intravenous glucose tolerance tests. Although BMI was the main contributor to S_i, AN also independently contributed to S_i. In contrast to our findings, Nguyen et al[20] found that once corrected for adiposity, AN was no longer associated with insulin resistance as measured directly with frequently sampled intravenous glucose tolerance tests. However, the study population was younger (6 to 10 years of age), limited to African-American and Caucasian youth, and had smaller sample sizes.

Our study results suggest youth, 8 to 14 years of age, with AN have significant insulin resistance, and more than 1 in 4 will already have evidence of abnormal glucose homeostasis. The 3 independent risk factors for having IGT in our subjects with AN, parallel established risk factors for the development of diabetes: severe insulin resistance, female sex, and GAD autoimmunity, potentially causing an impairment of insulin secretion. Identifying youth with AN in the primary care setting may allow for implementation of appropriate interventions that have the potential of attenuating, if not preventing, the development of diabetes mellitus and metabolic abnormalities. ■

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