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Brief report

Hypercholesterolemia in Asperger syndrome: Independence from lifestyle, obsessive–compulsive behavior, and social anxiety

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Abstract

We report on elevated total cholesterol and low-density lipoprotein (LDL) levels in 22 individuals with Asperger syndrome compared with well-matched controls, after accounting for lifestyle variables and clinical symptomatology that could affect them. A potential role for dyslipidemia in the pathogenesis of some forms of autism is discussed.
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1. Introduction

Asperger syndrome (AS) is a neurodevelopmental disorder belonging to the autism spectrum. It is characterized by impairments in socialization and ritualistic and stereotypic behaviors. While its etiology remains unknown, genetic and early developmental factors are considered key.

Several studies in recent years have reported abnormalities in lipid profiles in psychiatric disorders such as depression (Huang et al., 2003), bulimia nervosa (Monteleone et al., 2005), and generalized anxiety disorder (Sevincok et al., 2001). Interestingly, elevations in cholesterol levels have also been reported in conditions that share clinical features with AS, such as obsessive–compulsive disorder (e.g. Peter et al., 2002) and social anxiety (Landen et al., 2004).

In this study we contrasted for the first time lipid profiles of individuals with AS with those of well-matched control subjects. We also sought to examine if potential group differences could be explained by social anxiety and obsessive–compulsive behavior.

2. Methods

We analyzed data from 22 patients with AS and 22 healthy controls matched for age, gender, body mass index (BMI), and education, who were part of a study on AS and social cognition. AS individuals were recruited through local AS support groups or were referred by specialized clinicians. Diagnoses were confirmed for all AS participants according to DSM-IV AS criteria, and clinical symptoms of autism were assessed with the Autism Diagnostic Interview-Revised

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(ADI-R) in 16 subjects with available parental informants. Individuals in the control group were healthy volunteers participating in ongoing studies of normal aging at the NYU School of Medicine Center for Brain Health.

The research protocol was approved by the ethics committee of the New York University School of Medicine, and all participants gave written informed consent. Any history or present evidence of significant neurological or medical disease (as determined for all study participants by neurological and physical examination, and brain MRI) led to exclusion from the study. None of the AS or control subjects were taking cholesterol-lowering drugs or medications with known effects on lipid levels (e.g. corticosteroids, estrogens, androgens, beta-blockers, and typical or atypical antipsychotics).

A blood sample was obtained after a 12-h overnight fast to assess total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride (TG) levels, CBC, liver profile, electrolytes, thyroid functions, and glucose levels. Lipid profiles were established utilizing enzymatic methods and standard equipment (Vitros-950; Johnson and Johnson, New Jersey, 2003). We assessed intellectual functioning with the Shipley Institute of Living Scale (Prado and Taub, 1966), comprising a vocabulary and an abstract thinking test. Based on a sum of the raw scores of the tests, Wechsler Adult Intelligence Scale-Revised full scale IQ was estimated using published procedures (Zachary et al., 1985).

In a post-study survey, dietary habits were assessed with Block's brief food screener (Block et al., 2000). Furthermore, each subject's physical activity was estimated using the International Physical Activity Questionnaire (IPAQ)-Short Form (Craig et al., 2003). In addition, we assessed tobacco smoking/non-smoking status. We measured social anxiety and obsessive–compulsive behavior with the Liebowitz Social Anxiety Scale-Self Report Form (LSAS-SR) (Oakman et al., 2003) and the Short Version of the Obsessive–Compulsive Inventory (OCI-R) (Foa et al., 2002).

The post-study survey was returned by 16/22 AS subjects and 16/22 controls. Responders and non-

Table 1
Background variables and lipid profiles for Asperger ($n=22$) and control subjects ($n=22$)

	Asperger	Control	t (df)	P
Gender (male/female)	17/5	17/5		1.00 [a]
Age (years)	40.8±10.8	44.6±14.8	0.99 (42)	0.33
Education (years)	16.7±1.7	16.4±1.6	305 [b]	0.325 [b]
Intellectual functioning (SILS score)	68.1±8.5	70.0±6.5	1.05 (42)	0.42
BMI (kg/m^2)	26.3±4.8	24.9±4.1	−1.08 (42)	0.28
Systolic blood pressure (mm Hg)	124±14	119±16	−1.08 (42)	0.29
Diastolic blood pressure (mm Hg)	76±10	74±10	222.5 [b]	0.61 [b]
Fasting glucose (mg/dl)	79±8.9	79±9.3	−0.02 (42)	0.98
12 h urinary cortisol (μg/vol)	11.9±7.8	13.9±12.5	0.60 (42)	0.55
Smoking [c] (non-smoker/smoker)	16/0	15/1		1.00 [a]
Physical exercise [c] (MET)	2059±1304	3155±2014	1.83 (30)	0.08
Saturated fat [c] (g per day)	26.8±7.4	24.5±8.8	−0.80 (30)	0.43
% fat [c] (daily % of total calories)	33.1±6.1	31.0±5.2	−1.08 (30)	0.29
Dietary cholesterol [c] (mg per day)	271±71	251±87	−0.71 (30)	0.48
Dietary fiber [c] (g per day)	17.7±5.2	19.9±4.8	1.29 (30)	0.21
OCI-R [c] (total score)	25.2±10.5	12.3±8.0	−3.92 (30)	0.001
LSAS-SR [c] (total score)	33.6±14.8	13.2±9.2	−4.68 (30)	0.001
Total cholesterol (mg/dl)	195.0±31.0	171.8±24.8	−2.75 (42)	0.009
Cholesterol cut-off [d] (below/above)	11/11	20/2		0.007 [a]
HDL (mg/dl)	45.5±10.9	53.6±13.4	2.20 (42)	0.034
LDL (mg/dl)	124.3±27.9	101.9±22.8	−2.91 (42)	0.006
Triglycerides (mg/dl)	126.2±66.8	81.5±38.2	−2.73 (42)	0.009

Values are means±standard deviations.

Abbreviations: SILS=Shipley Institute for Living Scale; MET=multiples of the resting metabolic rate; OCI-R=Obsessive–Compulsive Inventory-Revised; LSAS=Liebowitz Social Anxiety Scale-Self Report.

[a] P established by two-sided Fisher's exact test.

[b] Test values (U) and P were established by Mann–Whitney U-test.

[c] =for Asperger ($n=16$) and Control ($n=16$) with available questionnaires.

[d] Cut-off for cholesterol (>200 mg/dl) according to NCEP guideline.

responders did not differ significantly on any of the variables reported here.

3. Results

All variables were tested for normal distribution with the Kolmogorov–Smirnov test. To ascertain between-group differences, only variables that displayed normal distribution were studied with independent sample two-tailed *t*-tests. Data that were either not normally distributed or categorical were analyzed by Mann–Whitney *U*-tests or Fisher's exact test, respectively. Statistical analyses revealed no significant group differences in age, gender, education, intellectual functioning, BMI, smoking, blood pressure, fasting glucose, or any of the dietary variables. However, AS subjects showed a trend towards lower physical activity and reported significantly higher levels of social anxiety and obsessive–compulsive symptoms (see Table 1).

AS subjects showed significantly elevated levels of TC, LDL, and TG and significantly lower levels of HDL compared with controls (Table 1). After controlling for physical activity in univariate analyses of covariance, group differences remained significant for TC ($F(1, 29)=6.549$, $P=0.016$) and LDL ($F(1, 29)=6.371$, $P=0.017$) but not for HDL ($F(1, 29)=1.012$, $P=0.323$) and TG ($F(1, 29)=1.592$, $P=0.217$).

To examine if group differences in social anxiety and obsessive–compulsive behavior accounted for the differences in lipid profiles between AS and healthy controls, we controlled for these variables in a second set of analyses. However, in these analyses, all between-group differences in lipid profile remained significant: TC ($F(1, 28)=6.923$, $P=0.014$), LDL ($F(1, 28)=7.463$, $P=0.011$), HDL ($F(1, 28)=5.680$, $P=0.024$), and TG ($F(1, 28)=7.794$, $P=0.009$).

4. Discussion

To our knowledge, this is the first study on lipid profiles in psychiatric disease that has ruled out the confounding influence of diet, exercise, medication, and smoking. We found elevated levels of total cholesterol, LDL, and triglycerides, and significantly lower levels of HDL in patients with Asperger syndrome relative to healthy controls. Literature has described modifying effects of exercise on HDL and TG (e.g. Durstine et al., 2002). Therefore, given that we had a trend for exercise to be higher in the control group, when we controlled for exercise, we found that only the group differences in HDL and TG levels were affected; group differences in total cholesterol and LDL levels remained significant.

As expected, our groups differed on social anxiety and obsessive–compulsive behavior, which are symptoms associated with a diagnosis of AS. Because elevations in lipid profiles have been reported in social anxiety and obsessive–compulsive disorders (Landen et al., 2004; Peter et al., 2002), we were interested in testing if our group differences in lipids were due to a non-specific association with those symptoms. We found that the observed differences in TC and LDL were independent of social anxiety and obsessive–compulsive behaviors.

It is tempting to speculate that dyslipidemia is linked to the pathogenesis of AS. There is some indirect support for such an etiological association. First, adequate cholesterol levels are crucial for serotonin metabolism and myelination of the brain, both of which have been reported to be abnormal in autism (Herbert et al., 2004; Chugani, 2004). Cholesterol is indispensable for the development of serotonergic CNS neurons and for the catabolism and transport of serotonin. Studies in humans indicate a positive relationship between cholesterol and serotonin levels (Steegmans et al., 1996), and hyperserotonemia is frequently observed in autism spectrum disorders (e.g. Coutinho et al., 2004), including AS (Mulder et al., 2004). An early increase in head and brain size is one of the most consistent neurobiologic findings in autism (Brambilla et al., 2003), and this appears to be driven mainly by excessive myelination (Herbert et al., 2004). Interestingly, experimental hyperlipidemia results in accelerated myelinogenesis in laboratory animals (Salvati et al., 2000).

Other indirect support for the link comes from the neurodevelopmental disorder Smith–Lemli–Opitz syndrome (SLOS). Due to a genetic defect, affected individuals have low cholesterol and abnormally high 7-dehydrocholesterol levels. Interestingly, about 50% of SLOS patients meet diagnostic criteria for autism (Tierney et al., 2001). Furthermore, it has been suggested that autism may be a disorder of fatty acid metabolism. Clark-Taylor and Clark-Taylor (2004) report on an autistic case with elevated lipids secondary to a dysfunction in fatty acid β-oxidation, which is in line with our findings.

In conclusion, abnormalities in cholesterol metabolism may have relevance for the etiology of AS. Further research is needed to replicate this first report and to explore potential mechanisms. Given that AS is a developmental disorder, future studies on lipid levels should be extended to include affected children. Moreover, it remains to be established if this hypercholesterolemia is specific to AS or is present more broadly within the autism spectrum.

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