Aberrant Cholesterol and Lipoprotein Levels in Aggressive Male Adolescents

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aberrant cholesterol
Aberrant Cholesterol and Lipoprotein Levels in Aggressive Male Adolescents

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Abstract

Background: Cholesterol plays many important structural and functional roles in the brain, but because it likely does not cross the blood-brain barrier, brain cholesterol is synthesized de novo within the central nervous system. Its roles include activation of the signaling protein sonic hedgehog (shh), a morphogen that plays a key role in brain development. It also is fundamental to maintaining the integrity of neuronal membranes, especially in the exocytotic transport of serotonin vesicles into the synaptic cleft. It is believed to be the signal for synaptogenesis, and is a key component of myelin. In adults, hypocholesterolemia has been associated with an increased risk of aggression and violence.

Method: Blood cholesterol levels and lipoproteins were evaluated in 50 adolescent males (mean age = 15) admitted to a neurodevelopmental disorders unit, where the chief presenting problem was aggression. Cholesterol and lipoprotein levels were routinely measured in patients admitted to the unit.

Results: The mean cholesterol level of these patients was found to be at the 25th percentile for the general adolescent population and differed significantly from the distribution in historical controls. A curvilinear (cubic) relationship obtained between low-density lipoprotein and total cholesterol levels; it was posited that the former is most strongly associated with aggression.

Conclusions: The question remains as to whether aggression is directly related to low cholesterol or indirectly via interactions with such variables as serotonin receptors and neuromodulatory steroids.

Introduction

Low Cholesterol: Ideal or Risk Factor?
The societal obsession with preventing heart disease by aggressive pharmacologic management to lower cholesterol levels has led to widely publicized (if controversial) recommendations such as those of the recent Jupiter study arguing for the use of statins even among adult patients without elevated LDL levels (1). Also—despite the fact that some statins cross the blood-brain barrier—obese and hyperlipidemic pediatric patients as young as age 10 or even 8 years have been proposed as appropriate subjects under some circumstances for administration of statins (2,3). Hypcholesterolemia which may result from aggressive cholesterol lowering with statins and other means may, however, have adverse effects. We present data on hypocholesterolemia in aggressive adolescent males, and review the literature on hypocholesterolemia and behavior.

A low—or insufficient—cholesterol level may in and of itself be a significant risk factor for behavioral disorders including those marked by aggression and violence among children and adolescents. This has already been demonstrated on numerous occasions for adults, in which an overwhelming number of studies show a relationship between hypocholesterolemia in the absence of cholesterol-lowering therapy and aggression, violence, and suicide (4,5,6,7,8). Additionally, several studies have suggested that suicide rates rise with lower cholesterol levels (9,10,11,12,13). A large Swedish study found that men with below-average blood cholesterol levels at baseline were more likely to commit violent crimes (14). Several innovative studies have also reported on the effects of severe hypocholesterolemia in adults with genetic disorders such as abetalipoproteinemia or Smith Lemli Optiz syndrome (15, see also Sikora et al (16) for the high incidence of autism in SLOS patients, and Lalovic et al.,(17) for high prevalence of suicidality in relatives of patients with SLOS).

So far, however, there is relatively little information available on the adverse effects of hypocholesterolemia in children and adolescents. There are a few studies of children and adolescents with genetic disorders (18,9,20) that basically parallel the findings in the adult literature. Among non-syndromic general psychiatric populations, the literature is even sparser, though several studies have documented associations between hypocholesterolemia (cholesterol levels < 160 mg/dl) and aggression and suicidal ideations (21,22, 23). The paucity of data in this potentially critical clinical area is largely what motivated the present study.

Cholesterol in the Brain: A lynchpin for many key structures and processes

In all these studies, blood cholesterol levels are used as a surrogate for brain cholesterol levels. As a
hydrophobic substance, pure cholesterol is not directly soluble in the blood, and is therefore transported by lipoproteins, which are too large to cross the blood-brain barrier. Uptake from plasma of LDL- or HDL-cholesterolester into the mammalian brain has not been observed in vivo (24). The brain however is the most cholesterol-rich organ in the body, reflecting the significant role cholesterol has come to play in neuron structure and function during the course of evolution, and it appears that cholesterol needed by the brain is produced through de novo synthesis (mainly from acetyl-CoA) within the CNS itself (25). On this basis, one might question the rationale for cholesterol supplementation in SLOS to improve neurodevelopment given that cholesterol does not cross the blood brain barrier (BBB) (26,27,28,29).

Low brain cholesterol levels found in genetic disorders where there is inadequate production of cholesterol or disruption of synthesis have profound consequences on the development of the central nervous system. For instance, cholesterol has an important role in activating sonic hedgehog (shh), a ligand of the hedgehog signaling pathway which plays the role of a morphogen—a molecule that diffuses to form a concentration gradient and whose effects on cells during development depends on concentration. Shh plays key roles in vertebrate organogenesis, including brain organization and the growth of digits, but its activation depends on cholesterol forming a covalent bond with shh. Difficulty in forming this bond in individuals with genetic disorders affecting cholesterol biosynthesis may account for some of the abnormalities found in Smith-Lemli-Opitz Syndrome (SLOS) in which impairment of the last step of cholesterol biosynthesis leads to markedly low plasma and tissue concentrations of cholesterol (30). SLOS patients variably show multiple malformations, intellectual disability, autism, and sometimes abnormal brain development (31,32). Also, SLOS carriers have been found to have increased incidence of aggression and suicidality (19). Patients with idiopathic autism generally have also been found to have low cholesterol levels (33), though so far cholesterol metabolism has not been systematically studied in such patients nor specifically linked to abnormalities of brain development. Additionally, some work involving zebrafish as experimental subjects suggests that fetal alcohol spectrum defects (FASD) may also be linked to disruption by alcohol of shh cholesterol modification. Supplementation of alcohol-exposed zebrafish embryos with cholesterol rescues the loss of shh signal transduction and prevents the development of FASD-like effects (34).

More broadly, and as demonstrated only in the past decade, cholesterol is the signal for synaptogenesis (35). The mechanisms by which this occurs are only now being elucidated. A key concept is that of lipid rafts—cholesterol/sphingolipid microdomains in the plasma membrane, which are important in maintaining synapses, dendritic spines, and surface AMPA receptors. Depletion of cholesterol in cultured hippocampal neurons (by treating neurons with fumonisins B1 and mevatastin) is found to produce loss of both inhibitory and excitatory synapses and dendritic spines (36). In addition to compromising shh signal transduction as described above, low plasma and tissue concentrations of cholesterol may result in lower density of synapses and spines leading to a coarsening of those that do develop. There is, further, an increasing body of experimental evidence demonstrating that neurons have the capacity to respond to disturbances in synaptic function or altered innervation and thereby maintain their function within a normal physiological range. Even following traumatic brain injury (TBI) or acquired brain injury (ABI), new neurons can be generated and integrated into existing circuits, and the strength of neurotransmission can be modulated to allow activation across remaining synapses. Moreover, the human brain overproduces synapses (synaptogenesis) such that a selection from the excess pool of synapses can be made to facilitate adaptation. Cholesterol may thus play a critical role in determining the response of the brain to trauma.

Finally, hypocholesterolemia may be associated with incomplete myelination, especially of those regions of the brain that are last to myelinate, such as the frontal lobes (37). An autopsy study of violent vs. non-violent suicide completers found that violent suicide completers had lower grey-matter cholesterol content in orbitofrontal cortex and ventral prefrontal cortex (38). Therefore, there is good reason to suspect that hypocholesterolemia can adversely affect the brain, and that this may be a link between hypocholesterolemia and adverse behavior.

**Cholesterol, aggression and violence: The serotonin connection**

Despite the fact that pure cholesterol does not cross the blood-brain barrier and the brain has its own machinery for de novo cholesterol metabolism, blood cholesterol levels may still affect behavior indirectly. The diverse manifestations of aggressions may be related to a number of different mechanisms of motivation, behavior, and function, as mediated by a wide array of neural and neuroendocrine pathways. The role played by the neurotransmitter serotonin (5-HT) has been subject of much research, with a number of studies documenting the relationship between low brain concentrations of 5HT and violent
and suicidal behaviors (39,40,41,42,43,44). Crucially, cholesterol appears to play a major role in modulating the serotonin system. One possible evolutionary explanation for this association is provided by the cholesterol-serotonin hypothesis, first derived from work on non-human primates documenting increased non-ritualized aggression in association with a diet low in saturated fat and cholesterol and decreased cerebrospinal serotonin concentrations (45,46,47).

At a molecular level, the effects of cholesterol on the serotonin system may be mediated through the role played by cholesterol in maintaining the integrity of plasma membranes. In the mature brain cholesterol is part of the exocytosis apparatus in presynaptic terminals and of the biogenesis and transport of synaptic vesicles; moreover cholesterol-rich domains are found at vesicle membranes and seem to be critical in axonal transport along microtubules. Cholesterol directly modulates receptor function by changing membrane fluidity and/or specific molecular interactions (48). In the mouse, membrane fluidity markedly modulates binding of serotonin to receptors (49). Cholesterol also appears to promote cell adhesion between postsynaptic and presynaptic ends (50) and has been identified as the signal for synaptogenesis. Thus, cholesterol plays a major role in the serotonin system by exerting influence at a number of control points (35). Though the way in which blood cholesterol influences and acts on central serotonergic systems (especially the rhomboencephalic raphe nuclei from which serotonergic fibers project into areas of the cerebral cortex) is not precisely known, it does appear, as first suggested by Engelberg (51), that low blood cholesterol may induce low central cholesterol and reduce lipid microviscosity of neuronal cell membranes, leading to changes in 5HT receptor exposure and changes in the turnover rate of synaptic 5HT transport.

A sexually dimorphic sensitivity to these effects has recently been postulated by Wallner and Machatschke (52). They point out that the larger brains of men are likely to be affected earlier by shortages of high-energy, cholesterol containing food sources, and that scarcity of these may influence the central cholesterol metabolism either by: 1) reducing supply of glucose, causing a decrease in de novo brain synthesis of cholesterol; and 2) by reduced uptake of lipoprotein-cholesterol complexes through the blood-brain barrier, which may result in destabilization of plasma membranes resulting ultimately in serotonin transporter (SERT) activity, impaired binding of the serotonergic receptor subtypes 5HT1A, 5HT1B, and 5HT2A, and decreased 5HT re-uptake at pre-synaptic membranes. The end result being that serotonin levels are decreased in pre-synaptic neurons and in the synaptic cleft.

Undoubtedly, steroids with neuromodulatory effects also play a role (and cholesterol, of course, is the precursor for steroid hormone synthesis). Most pertinent here are the effects of the sex steroid testosterone, which was long believed to be the main determinant of male (and female) aggression. Though more recent research has given priority to the importance of low central serotoninergic activity in aggression, some research has indicated that testosterone may facilitate aggression in subjects with low 5H1AA titers (53). In conclusion, cholesterol plays many key roles in brain development and is indispensable for maintenance of essential structures and processes. Despite the fact that most published studies have involved animals or adult human subjects, there is overwhelming evidence to believe that hypcholesterolemia may have particular significance in children and adolescents in whom the brain is still developing and also that low cholesterol may be an significant, though often unappreciated, risk factor for behavioral disorders involving aggression, violence, and suicide.

Methods

This research was conducted as a retrospective chart review. The Minnesota Department of Human Services (MN DHS) institutional review board approved all procedures and all the participants or their guardians provided written consent for the use of their medical records in accordance with federal and state guidelines for research involving human subjects. The first author (W.S.) was in charge of supervising a unit for adolescent males with neurodevelopmental disorders in Minnesota. As part of the routine admission orders, fasting total serum cholesterol, LDL, and HDL levels were obtained for all patients admitted from November 2007 through April 2009. The chief criterion for admission was severe aggressions and inability to be stabilized on acute psychiatric units or residential facilities. Many of the participants in the study were already on psychotropic medications, and they presented with a variety of diagnoses. About half had Pervasive Developmental Disorder with concomitant diagnoses of Intermittent Explosive Disorder or Impulse Control Disorder NOS (which reflected their histories of episodic aggressions). The rest were diagnosed with a hodge-podge of mood disorders, including depression and bipolar; seizure disorders; TBI; fetal alcohol syndrome; oppositional-defiant disorder, and schizophrenia. We
had no confidence in the reliability of these diagnoses as they were made by a variety of clinicians in the community and many of the diagnoses changed during the course of their hospitalizations. We were not particularly concerned about the details of the diagnoses. All of the participants had extensive histories of attempted treatment with psychotropic medications, and most were still on those medications when they were admitted to our unit. The medications included, in rank order of preference: atypical antipsychotics (Olanzapine, Risperidone, Quetiapine, Aripiprazole, Ziprasidone), anticonvulsants, especially Valproate; and antidepressants, including Trazadone, often used for sleep induction, Selective Serotonin Reuptake Inhibitors, and Venlafaxine. Most were on polypharmacy at the time they arrived. None was naïve to medications and none presented with no medications. A number of these drugs—including the atypical antipsychotics that are widely used in this vulnerable population—have been associated with substantial weight gain even within only 10 weeks of initiation of treatment, ranging from 9.7 pounds for aripiprazole to 18.7 pounds for olanzapine (54,55). Elevations of lipids associated with the use of these drugs are also significant, and again appear to be greatest with olanzapine (LDL increased by more than 40 mg/dl in 21.6% of adolescent patients, the total cholesterol level increased by more than 40 mg/dl in 78% of these patients (56)). In interpreting the results of this study, it is important to bear this in mind, as the lipid levels of this sample were presumably systematically elevated owing to medication effects—though a detailed analysis would be necessary to work out all the possible effects, since some can cause low cholesterol and interfere with cholesterol synthesis as well, a potentially deleterious in pediatric and adolescent patients given the importance of cholesterol synthesis to brain just described (57).

Participants
As noted, this was a retrospective chart review. Total cholesterol levels were available for 50 patients; high density lipoprotein (HDL) results were obtained for all 50; low density lipoprotein levels (LDL) were available for 48 patients. All were male. Their ages ranged from 5 though 21 years old, with a mean of 15 and a standard deviation of 3. The participants had reasonably good appetites and were described as sufficiently well-nourished. None of the patients was taking a statin or other agent to lower cholesterol levels. Though lipids were routinely obtained on admission to our unit, only 2 (< 5%) had had lipid levels noted in previous laboratory screenings from referring or previous hospitalizations, and none had lipid levels obtained in emergency rooms or hospitals where they were “stabilized medically” prior to admission. This, unfortunately, seems to be fairly consistent with standards of practice both in community settings and even in psychiatric inpatient units at most hospitals where it is unusual to obtain lipid levels despite the already high (and increasing) use of atypical antipsychotic medications with this population and their propensity to elevate lipids and cause weight gain. There was no concurrent control group. Instead, we compared our results to population norms based on CDC data (23), in which the mean cholesterol level for adolescent males was 160 mg/dl with the lowest quartile being <145 mg/dl.

Results
As depicted in the descriptive data in Table 1, the mean cholesterol level was 145.88, approximating the lowest quartile of the Zhang et al., (23) normative data. The relationship between total cholesterol levels and LDL was best described by a cubic function with two curve changes in the slope of the regression line. This is shown graphically in the scatter plot presented in Figure 1. As shown in Table 2, the cubic relationship was statistically reliable. It should be noted, however, that cubic relationships are quite rare and that this finding might simply be the result of sampling error (58). Nevertheless, it is an intriguing finding and is discussed below.

Discussion
Despite the fact that most of these patients had prior histories of treatment with medications, especially atypical antipsychotics, which would be expected to increase their total cholesterol and LDL levels based on previous studies, this population as a whole showed significant hypcholesterolemia. Given the importance of cholesterol in brain development, the association of low cholesterol with some brain abnormalities, and the correlation noted in a number of adult and a few adolescent studies linking low cholesterol to aggressive behaviors, this finding appears to be rather significant, and has clear implications both for understanding the etiology of some brain abnormalities and problematical behaviors as well as for their treatment.
admission criteria) for significant problems of impulsive aggression. Thus, the finding of significantly lower blood cholesterol levels study among participants compared to controls was consistent with numerous studies in adults and several in adolescents indicating a relationship between low blood cholesterol levels and aggression. In addition to total cholesterol, we independently evaluated LDL and HDL levels. One unexpected finding was that 10, or 21% of our subjects, had HDL: LDL ratios of between 1.0 and 1.1, which, on the face of it, would seem to imply that HDL—i.e., cholesterol leaving cells—was nearly the same as LDL, cholesterol entering cells. Presumably, these individuals would have difficulty incorporating cholesterol into membranes or other cell constituents. The mean LDL in our patients was only 75.6, with a significant number (22, or 48%) having LDL levels below 70. This finding may suggest that these patients had decreased synthesis of cholesterol.

The form of the relationship between LDL and total blood cholesterol was curvilinear how is this different from cubic? An initial positive slope is followed by a negative slope at moderate elevations on both variables and returns to positive at higher values. Though we do not have a specific explanation for the shape of this curve, we speculate that the tail on the low-end, reflecting the presence of data points for patients with Pextremely low LDL values, may represent those with significant defects in cholesterol synthesis (for example, an inability to covert 7-dehydrocholesterol, 7-DHC, to cholesterol, as is seen in Smith-Lemli-Opitz syndrome). These are definitely the individuals in whom further studies need to be done, as they most likely represent the extreme cases in which the specific nature of genetic, metabolic, and other abnormalities can be identified. The tail at the high-end could reflect either an induced metabolic syndrome related to medication effects or defective receptor binding as in the hyperlipidemias. However, given the complex interactions of cholesterol with other variables, there are also other possibilities. As mentioned in the introductory section, a complex interplay was believed to exist between aggressive behavior, the 5HT system, and steroids with neuromodulatory function such as testosterone. (In a follow-up study to this one, which would have to be done as a prospective study, it may be worthwhile to test testosterone and other steroid hormone levels.) Elevated testosterone—whose synthesis is ultimately derived from cholesterol—may be associated with dominance behavior and competitive aggression (59) during challenging lifetime situations (60) or critical developmental phases. However, the relationship of dominance and traits such as sociopathy to testosterone levels also appears to be non-linear and instead to follow a curvilinear relationship. It is also likely that the relationship of blood cholesterol to central serotonergic activity is complex. There were a number of limitations to this study. First of all, it was a retrospective study. As a result there were a number of potentially confounding variables. One of the most important is contamination of the sample with medications (especially atypical antipsychotics whose perturbative effects on lipid levels are well documented even though they seem to be poorly monitored by clinicians). Also there was considerable heterogeneity in the sample based on the fact that the patients had a hodge-podge of (often poorly characterized) clinical diagnoses. The common denominator of aggression was noted; however, as we have noted, aggression is itself a construct that needs to be carefully defined and perhaps quantified. A future study of prospective patients in which these variables are more carefully controlled would be useful. Despite the limitations of the study, we did establish that aggressive adolescents on our inpatient unit exhibited cholesterol levels that were significantly below the mean for the control population. We suggest, as a question deserving further study, investigating whether our finding that low LDL may be an even more robust indicator of potential for aggression than low total cholesterol. It would also be useful to investigate the relationship between blood cholesterol and LDL and other metabolites such as urinary 5HT metabolites and testosterone and other steroid hormone levels. If it were practical, it would be useful to exclude from the study participants with significant histories of exposure to lipogenic drugs (especially the class of atypical antipsychotics), though admittedly this would present difficulties in any naturalistic study, and especially in a tertiary care setting such as our unit, given that atypical antipsychotics are often the mainstay of treatment for individuals with severe aggressions. It may be supposed that, even as low as they are, the total blood cholesterol and LDL levels found in this study underreports the size of the effect, since the medications being used all tended to increase, not decrease, lipid levels. We postulate that drug-naïve patients would likely have had lipid levels lower, perhaps even substantially, lower. However, it is also possible that some patients would have cholesterol synthesis disrupted by these drugs, and it is also possible that peripheral cholesterol metabolism would decouple, under certain conditions, with CNS de novo cholesterol synthesis. It would also be useful to investigate correlations between the total blood cholesterol and LDL levels.
and the intensity or severity of aggression. This, however, would not be entirely straightforward, as unfortunately, the psychological construct of aggression and related measurement issues are complicated. An inference about behavior being “aggressive” cannot be made on the basis of adverse consequences alone, for example. There must be a volitional intent to cause physical or social damage; accidental occurrences of this type are not aggressive. Definitions of aggression often include the intent to hurt or irritate. Under this rubric, such behaviors as whining would be classed as aggressive. Further, the intention to hurt or irritate might involve “not behaving in response to a request, for instance, so-called “passive aggression.” Additionally, there may be several dimensions of aggressiveness from person-centered or “hostile aggression” to behaviors that may hurt or irritate in order to obtain an important goal (i.e., instrumental aggression) (61). It is possible the strength and type of relationship between cholesterol and aggression may depend on the nature of the aggressive acts that constitute the dependent variable measure.

It remains unclear whether low blood cholesterol levels are a risk-factor for aggression independently of the specific cause; i.e., a genetic-metabolic disorder, such as Smith-Lemli-Opitz, versus low cholesterol related to food deprivation or other physiological events. Overall, the literature would seem to suggest that low blood cholesterol levels constitute a risk-factor regardless of specific etiology—though the relationship to aggression may, as described above, ultimately be mediated through other factors such as the serotonergic system.

Individuals with naturally occurring low cholesterol levels may—given the multifarious roles played by cholesterol in neurodevelopment—be at significant risk for delayed or impaired development. Though pure cholesterol does not cross the blood-brain barrier, it is possible, through some of the mechanisms mentioned earlier, that dietary intake of cholesterol and energy-rich foods may nevertheless stimulate brain cholesterol turnover rate and affect function of the central serotonergic system. It is significant that dietary cholesterol seems to be needed for maturation of mouse brain myelin (62). Also, early postnatal starvation has been associated with lasting brain hypomyelination (63). There is also growing interest in developing methods of smuggling molecules that do not cross the blood-brain barrier (such as glial-cell neurotrophic factor (GDNF) into the brain, and it is possible that eventually such methods could be devised to do so with cholesterol in patients with deficient de novo cholesterol synthesis in the CNS (64).

Might early detection of at-risk individuals (infants and toddlers with low blood cholesterol levels) and dietary supplementation offset neurodevelopmental delays and mitigate propensity for aggression? Though there is now general agreement on the basis of studies in rodents that the developing brain is capable of synthesizing all of the cholesterol required, and because studies have shown that little cholesterol in the brain comes from exogenous sources (26), it still remains an open question whether exogenous sources of cholesterol may not indirectly affect cholesterol accumulation and synthesis in the brain. At least a few studies using rodents and pigs have indicated that cholesterol feeding in the diet may increase brain cholesterol and/or myelin (62,65,66; but see 27). The seeming inconsistencies among these studies may be resolved if brain cholesterol synthesis is increased by a humoral and/or neural signal in response to cholesterol ingestion. Consistent with this, the presence of LDLR and HMG CoA reductase mRNA in the developing pig brain hints that brain cholesterol accretion may be modulated by both endogenous cholesterol synthesis in, and exogenous cholesterol uptake by, the central nervous system (66). Studies involving the effects of exogenous cholesterol supplementation on human subjects are so far quite scarce; though it is plausible that cholesterol in human milk may be important for brain development, the hypothesis so far remains untested (67), while exogenous cholesterol supplementation in patients with Smith-Lemli-Opitz syndrome has not by itself prevented the development of autistic symptoms in patients suffering from the disorder (16). Cholesterol and other dietary supplementation in patients with very low cholesterol remains a reasonable tactic, but is in need of additional research. Owing to difficulties modifying the dietary department’s regimens, we did not attempt it in the subjects of the present study. Apart from dietary interventions, it appears that the detection of low-cholesterol levels may help to predict, at least to some extent, responses to drugs. There has been considerable and justifiable concern about the dramatic weight gain and metabolic effects (including elevations in lipids) associated with medications such as atypical antipsychotics and Valproate, which are commonly used to treat aggression and mood lability, especially in children and adolescents. However, it may be that for those with cholesterol levels in the very low range maintenance or even elevation of lipid levels may be beneficial. There have been a handful of studies suggesting that the observed increase in mean serum cholesterol associated with certain medications may correlate with remission of depressive symptoms.
(68). Conversely, in one study looking at adult males with major depression, elevated cholesterol levels were associated with nonresponse to Fluoxetine treatment (69). Moreover, at a conceptual level, the metabolic syndrome itself has been described as being possibly the result of overstimulation of a system of interacting neurophysiologic and metabolic states that evolved to decrease the propensity for aggression. It follows that the metabolic syndrome may itself be not an unrelated set of side effects but a direct consequence of the anti-aggressive effects of certain drugs (70).

The main recommendation that emerges from of the present study is that—given that blood cholesterol levels, and perhaps LDL in particular, appear to be a risk-factor for aggressions in adolescents—lipids should be routinely screened. At present this does not appear to be standard practice, either in adolescent or adult psychiatric patients (and certainly not in children). Lipid levels, when they are obtained, are currently used only to monitor side-effects such as elevated lipids or metabolic syndrome in patients on atypical antipsychotics. Among the patients in this study, all of whom were referred to us from other programs, <5% had had cholesterol levels obtained from previous institutions. Even extremely low cholesterol levels were not flagged as risk factors for any conditions but were blandly regarded as “normal,” presumably on the basis that they did not contribute to increased risk for cardiovascular disease.

As our study showed—consistently with others—low plasma cholesterol levels, and especially LDL <70 and LDL:HDL ration approximating unity, appears to be as significant a risk factor among adolescents for neurodevelopmental disorders and aggression. Clinicians and researchers need to begin to pay attention to the fact that low cholesterol, especially among children and adolescents, may be as significant a risk factor for neurodevelopmental and behavioral difficulties as high cholesterol is for cardiovascular disease in adults. Certainly, an awareness of a pediatric patient’s cholesterol level offers an important piece of data with the potential to inform predictions about a patient’s risk of self-injurious behaviors, and further research may lead to more targeted interventions.

Some years ago, Tucker (71), in a somewhat critical review of the DSM diagnostic process used in psychiatry, lamented the fact that “as yet, we have no identified etiological agents for psychiatric disorders. Our diagnoses are nowhere near the precision of the diagnostic processes in the rest of medicine. While there are similar diagnostic processes in medicine, most medical diagnoses are based on objective findings; e.g., cancer is based on structural pathology, pneumonia on a bacterial or viral agent, and hypertension on the numerical deviation from a numerical norm.”

It would appear from an abundance of previous studies, including that presented here, that cholesterol is one objective finding with relevance to some of the behaviors—aggression, violence, and possibly suicide—of chief concern to psychiatrists and other mental health clinicians. It may well be a risk-factor as great for such behaviors as elevated cholesterol is for cardiovascular disease. Psychiatry has remained an orphan to the rest of medicine as we have no identified etiological agents for psychiatric disorders, and our diagnoses are nowhere near the precision of the diagnostic processes in the rest of medicine. In psychiatry, we also have had very few quantitative measures of anything to help advise us.

Cholesterol is one of the few objective measures we have in psychiatry with bearing on the conditions that concern us most, and we cannot afford to continue to ignore it. Low cholesterol should become for psychiatry what high cholesterol is for cardiology, and we should begin to take seriously the implications for the prediction of risks and their mitigation through possible treatments.

References

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Illustrations

Illustration 1

Descriptive Statistics

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Illustration 2

ANOVA for Cubic Regression

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Illustration 3

Satter Plot of Low Density Lipoprotein on Total Cholesterol
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