The Great Plains Laboratory, LLC

Cholesterol Deficiency:

A Major Factor in Autism and Other Chronic Disorders

Cholesterol is an essential sterol to life, found in every animal cell, which helps protect human tissues. Many people fear and focus on high cholesterol levels, as they are statistically associated with a greater risk of cardiovascular disease (CVD), yet little attention is paid to low cholesterol levels, which also can have serious health consequences. Like everything in nature, balance is key. Although very high blood serum cholesterol values are associated with heart disease, values that are low (below 160 mg/dL [4.14 mmol/L]) are associated with Autism Spectrum Disorder, increased violent behavior, suicide, depression, anxiety, bipolar disease,[3,4,5] Parkinson's disease, and increased mortality from cancer.

Most significantly, the death rate is doubled in older adults with lower total cholesterol, and stroke and cataract rates are higher. Low cholesterol values are also associated with manganese deficiency, celiac disease, hyperthyroidism, liver disease, malabsorption, and malnutrition. Pregnant women with low cholesterol are twice as likely to have premature babies or babies with small heads. Surprisingly, high cholesterol protects against some infectious diseases like tuberculosis,[7] which has been uncommon in the USA since The Great Depression, during which there was a substantial lack of high cholesterol foods because of financial hardship. Vegetarians have a much higher incidence of tuberculosis than meat eaters. It is possible that the overemphasis on a low cholesterol diet may also be associated with the recent marked increase in cases of tuberculosis.

Benefits of Cholesterol

Cholesterol serves several important roles in metabolism: It is a key constituent of all cell membranes and provides the structural framework for vitamin D, adrenal and sex hormones, and brain myelin, as well as for bile acids which help digest fat and increase absorption of fat soluble vitamins. Most cholesterol is made in the liver and can be synthesized from either fatty acids or glucose. Cholesterol synthesized in the brain is the primary component of the myelin that surrounds each nerve cell as a protective sheath. Loss of myelin inevitably causes neurological damage. Both neurons and glial (support) cells in the central nervous system (CNS) require sufficient amounts of unbound cholesterol as an integral part of their cell membranes. Cholesterol is also essential for the activation of the developmental protein, "Sonic Hedgehog", which plays a role in cell growth and the shaping of the body in utero, especially the brain and central nervous system.

Why the Brain Needs Cholesterol

- There is a direct correlation between the concentration of cholesterol in the brain, particularly in the myelin, and how well the brain functions.
- The brain is the most cholesterol-rich organ in the body.
- In the central nervous system (CNS), essentially all (99.5%) cholesterol is the free or unesterified form (unattached to fatty acids).
- The majority (70%) of cholesterol present in the CNS is believed to reside in the myelin (the material that insulates the nerve fibers) sheaths and the plasma membranes of astrocytes (brain support cells) and neurons.
- Half of the white matter, which contains the nerve axons that allow for transmission of brain signals, may be composed of cholesterol-rich myelin.

Cholesterol and Cardiovascular Disease

High cholesterol may be associated with the development of CVD, but cholesterol may actually be deposited as a beneficial "patch" on inflamed or injured blood vessels, particularly coronary arteries. Macrophages scavenge cholesterol along with other cell debris and may become "foam cells" which accumulate in artery walls and cause atherosclerotic streaks. Assessments of inflammation such as C-reactive protein and Phospholipase A2 or homocysteine level (included in the Advanced Cholesterol Panel) have been suggested as better predictors of CVD risk.

Low Cholesterol Associated with Mental Disorders & Mortality in Elderly

Studying serious genetic disorders that prevent cholesterol synthesis can aid the understanding of the health consequences of low cholesterol. Low cholesterol has been associated with greater risk of suicide, violence, and mood disorders such as depression. Cholesterol levels influence serotonin activity in the brain. Serotonin is the neurotransmitter associated with mood, and low levels are associated with depression and violent and anti-social behavior. If cholesterol in the nerve cell membrane is deficient, serotonin may not properly bind to its receptor. Cholesterol also stabilizes receptors for the social-bonding hormone oxytocin. In the elderly, studies over several decades have pointed to increased risk of death in the population with the lowest cholesterol. Falling cholesterol in the elderly is a sign of increasing morbidity, with controversy over whether it is a sign of underlying chronic disease or a cause of disease.

Disorders Associated with Low Cholesterol

- Alzheimer's Disease
- Crohn's Disease
- Rheumatoid Arthritis
- Autism
- Depression
- Anxiety
- Hyperthyroidism
- Liver Disease
- Celiac Disease
- Bipolar Disease
- Alcoholism
- Lung Cancer
- Suicide
- Obesity Associated with Human Adenovirus-36 Infection

Cholesterol: The Good and The Bad

The concept of "good" and "bad" for dietary substances depends on the circumstances of the individual person. Much of the information that the public receives is oversimplified. To a person dying of thirst in the desert, any water is very good. To a person, who just drank two gallons of water on a dare, another glass of water might be fatal. The concept of good and bad cholesterol is similar to the water analogy. The type of cholesterol that is associated with high density lipoproteins (HDL), which help remove cholesterol from certain tissues is termed "good cholesterol". The type of cholesterol associated with low density lipoproteins (LDL), which transport cholesterol to tissues that require it is designated as "bad cholesterol". If, however, the tissues of a certain person have a significant overall deficiency of needed cholesterol, then both LDL and HDL cholesterol can be good for that person. Therefore, a purified cholesterol supplement cannot be inherently "good" or "bad" and the body will distribute it to the locations where it is needed the most. LDL cholesterol actually protects humans against infection. Deadly staphylococcus bacteria produce endotoxins that have the ability to kill human cells, including red blood cells. LDL has been found to protect human red blood cells from this toxic effect of endotoxin, while HDL was not protective. A study at the University of Pittsburgh found that in young and middle aged men, those that had LDL cholesterol below 160 mg/dL (4.14 mmol/L) had a significantly lower number (of total and various types) of white blood cells than men with LDL cholesterol above 160 mg/dL (4.14 mmol/L).

Advanced Cholesterol Panel

The Great Plains Laboratory has developed a special cholesterol-related panel that will help to determine whether cholesterol deficiency or abnormalities in cholesterol transport are present. The Advanced Cholesterol Panel includes the following markers: Total cholesterol, apolipoprotein A-1, apolipoprotein B, Lipoprotein (a), and homocysteine. Lipoproteins are involved in cholesterol, lipid, and vitamin E transport. Each of these markers, indicated in high or low levels, has been associated with a variety of genetic diseases of cholesterol metabolism including SLOS, Tangier's disease, and abetalipoproteinemia. Low levels have also been linked to Alzheimer's disease, Crohn's disease, rheumatoid arthritis, autism, depression, anxiety, hyperthyroidism, liver disease, celiac disease, bipolar disease, alcoholism, lung cancer, suicide, and obesity associated with human adenovirus-36 infection.

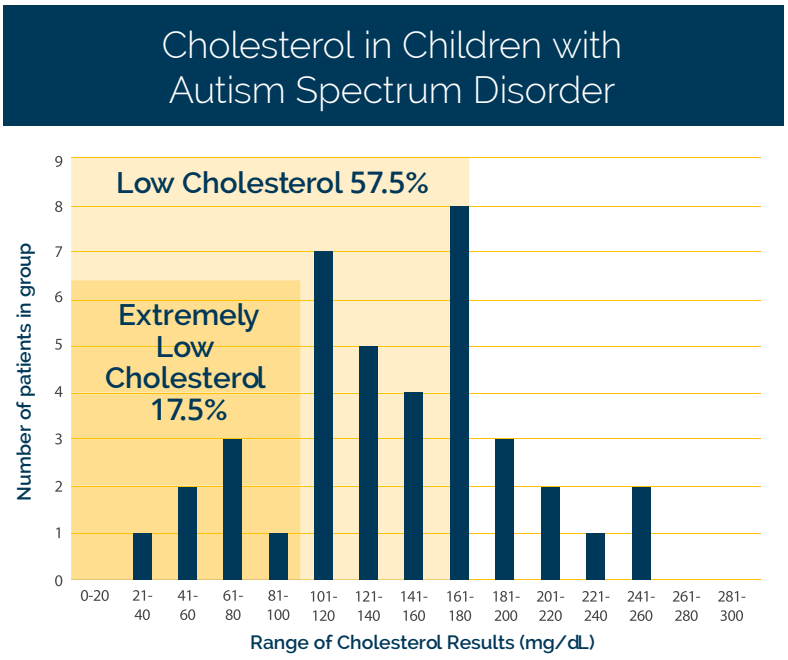
Cholesterol Deficiency: A Common New Factor In Autism

Dr. Richard Kelly, a research physician at John Hopkins University has found, along with his colleagues, that autistic symptoms prevalent in the genetic disorder SLOS (Smith-Lemli-Opitz Syndrome) quickly reversed after supplementation with dietary cholesterol. Some of the many improvements included sleeping through the night, overcoming aberrant behaviors, learning to walk, speaking for the first time, and becoming more responsive and social with family members. In addition, other benefits of cholesterol supplementation included a decreased rate of infections, reduced skin rashes, marked reduction in self-harming behaviors, improved muscle tone, decreased tactile defensiveness, more rapid growth, and improved behavior overall. Parents reported their children having significant decreases in Autistic behavior and even some non-verbal autistic adults spoke for the first time, all within days of taking cholesterol supplements. These changes occurred before cholesterol values had increased in the blood, which indicates that the improvements may be a result of cholesterol forming its derivatives, such as steroid hormones or bile salts.

Cholesterol Deficiency in All Autism Spectrum Disorders

Dr. Elaine Tierney directs the Autism Metabolic Research Program at the Kennedy Krieger Institute. Dr. Tierney and her colleagues involved in SLOS research wanted to determine if cholesterol deficiency is also common in "ordinary" autism.[1,2] They investigated the incidence of cholesterol deficiency in blood samples from a group of subjects with autism spectrum disorder (ASD) from families in which more than one individual had ASD, but not SLOS. Using highly accurate gas chromatography/mass spectrometry, cholesterol, 7-DHC and its related molecules were quantified in 100 samples from subjects with ASD. Although no sample had values consistent with SLOS, 19 samples (19%) had total cholesterol levels lower than 100 mg/dL (2.59 mmol/L)*, values that are much lower than those found in normal children of the same age. In addition, these researchers found that cholesterol was low, not as a result of excessive breakdown, but because of reduced production. *The units of measure used in the United States, Latin America, and Asia are mg/dL. Europe and Canada use mmol/L.

This work was confirmed at The Great Plains Laboratory which performed cholesterol testing on 40 children with Autism Spectrum Disorder. In this study, as in Dr. Kelly's study, extremely low cholesterol values are defined as the lower fifth percentile of normal children (less than 100 mg/dL [2.59 mmol/L]) which was determined in a nationwide study of the Center for Disease Control. The results of the two studies were similar, with The Great Plains Laboratory percentage of extremely low values being 17.5% versus 19% of values being low for the Tierney study. In addition, 57.5% had cholesterol values less than 160 mg/dL (4.14 mmol/L). NIH had concluded in 1990 from a meta-analysis of 19 studies, that men and women (to a lesser extent) with a total serum cholesterol level below 160 mg/dL (4.14 mmol/L), had approximately a 10% to 20% increased death rate compared with those with a cholesterol level between 160 to 199 mg/dL (4.14 to 5.15 mmol/L). Specifically, people with these lower cholesterol levels were more likely to die from cancer (primarily lung and blood), respiratory and digestive disease, violent death (suicide and trauma),[3,4,5] and hemorrhagic stroke.



It is interesting to note that in The Great Plains Laboratory study, only one child on the Autistic spectrum had an extremely high cholesterol level, with a value over 340 mg/dL (8.79 mmol/L).

The Link Between Sonic Hedgehog (SHH), Autism, and Cholesterol

Abnormalities in cholesterol metabolism present in SLOS and autism may also impair the function of a developmental signaling protein with the bizarre name "sonic hedgehog". Sonic hedgehog (SHH) is named after the character from the popular Sega Genesis video game. The original hedgehog gene was found in the fruit fly Drosophila and was named for the appearance of the mutant fly offspring in which the embryos are covered with pointy spines resembling

a hedgehog. The first two types of hedgehog proteins were named after certain species of hedgehogs and the third was named after the video game character.

Cholesterol must covalently bond to SHH before SHH can function properly.[6] In addition, some forms of SHH have both cholesterol and the fatty acid palmitic acid covalently attached to the protein. (Palmitic acid is required for the production of a soluble hedgehog protein complex and long-range signaling in humans). The attachment of cholesterol activates the sonic hedgehog protein and without adequate cholesterol, SHH protein function is impaired.

Functionality of Sonic Hedgehog (SHH):

- Plays a central role in developmental patterning, especially of the nervous system and the skeletal system.
- Important in the growth and differentiation of a variety of cell types, including the development of T cells in the thymus.
- Purkinje neurons secrete SHH to sustain the division of granule neuron precursors in the external granule layer in cerebral development. Abnormal cerebellar development and especially purkinje cell development has been associated with autism.
- As a transcription regulating protein, SHH alters which genes function at a given time.

SLOS and Autism

Smith-Lemli-Opitz Syndrome (SLOS) is an autosomal recessive genetic disorder associated with autism, multiple malformations, and mental retardation syndrome initially described by Smith, Lemli, and Opitz.[1,2,8] The syndrome (SLOS) is due to a deficiency of 7-dehydro-cholesterol (7DHC) reductase, the enzyme responsible for catalyzing the final step in cholesterol synthesis indicated in a simplified figure of cholesterol metabolism to the right. As a result of this enzyme deficiency, 7-dehydro- cholesterol accumulates and the level of cholesterol dramatically decreases. Although some children with SLOS have severe physical abnormalities, many are only mildly affected, and autistic behaviors may be their only major abnormality. Since the biochemical test for this disease is done so rarely, it may be possible that there are many other children with SLOS, with fewer anatomic abnormalities, in which the diagnosis is missed. As a result of this enzyme deficiency, individuals with this disorder have extremely low cholesterol values but extremely high values of 7-dehydrocholesterol. One person with SLOS had the lowest cholesterol value (< 1 mg/ dL [<0.03 mmol/L]) ever measured in serum while most Americans have values between 150-250 mg/dL (3.88-6.47 mmol/L).

Because cholesterol levels are insufficient in persons with SLOS, virtually none of the normal steroid hormones and bile salts derived from cholesterol can be adequately produced. However, abnormal forms of these hormones derived from 7-DHC can be produced instead. It is important to note that cholesterol is an essential element in myelin, which is the insulating material essential for nerve function (especially in the brain). Persons with SLOS will possess varying degrees of cognitive abilities ranging from borderline intellectual functioning to profound mental retardation. It is common for them to also exhibit sensory hyper-reactivity, irritability, language impairment, sleep cycle disturbance, self-injurious behavior, and autism spectrum behaviors. In one study, nearly 50% of children with SLOS met the DSM-IV criteria for autism. In another study, 86% of children with SLOS had an autistic spectrum disorder.[8] Many of the behavioral abnormalities of SLOS significantly respond to supplementation with cholesterol. If Autism is prevalent in SLOS, and the autistic symptoms improve with cholesterol supplementation, then it is conceivable that any severe biochemical abnormality leading to de-myelination needs to be explored as a possible cause of autism.

Cholesterol Doses to Treat SLOS

Doses of cholesterol used in therapeutic trials have varied from 20-300 mg/Kg body weight/day. In some SLOS treatment studies, supplemental bile acids were also incorporated into the diet. In early studies, 50 mg /Kg of pure crystalline cholesterol was used and showed beneficial results. Other options for cholesterol supplementation include use of egg yolk, whipping cream, and butterfat. A single egg yolk contains about 250 mg of cholesterol. A 100-Kg adult with SLOS would have to consume 40 egg yolks per day to consume enough cholesterol to attain a dose of cholesterol of 100 mg/Kg per day. In addition, organ meats like liver and kidneys are particularly rich in this compound. A 3 oz (85 g) serving of beef liver, for example, contains about 372 mg of cholesterol. A similar portion of brain from animal sources has close to triple this amount.

See www.greatplainslaboratory.com/advanced-cholesterol-profile for references

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