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Review

Autism and Cholesterol

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ABSTRACT

Autism spectrum disorder (ASD) is a disorder that develops as a result of some neuronal abnormalities. It may be caused especially during pregnancy, or genetic factors. In addition, communication problems and repetitive behaviors are characteristic symptoms. However, does not really have a specific treatment. Cholesterol, a crucial molecule for cells, has recently attracted attention for its impact on neurons and ASD. The function of cholesterol in brain development and its impact on inflammation should help researchers understand better how cholesterol affects ASD. Children with ASD have also been observed to have complications with cholesterol and lipid metabolism. These factors show that cholesterol may play a key role in ASD.

Keywords: Autism spectrum disorder, cholesterol metabolism.

The specific cause of ASD is uncertain. Even that, new scientific findings show that some disorders in cholesterol metabolism are associated with ASD. Cholesterol is an organic molecule that is essential for cells. It has an important role in nerve cells as in other cells. Sleep problems, intellectual disability, and anxiety have all been found in patients with ASD who already have an abnormal cholesterol metabolism. The treatment of cholesterol metabolism defects could be efficacious in the prevention of ASD.[1-4]

ASD is a developmental disorder that occurs in early childhood. It may affect social skills, communication, relationship, and self-regulation. It is usually determined in the first 3 years, and it continues for the whole of patient's life.[1,2]

The main cause of ASD is unexplained but is thought to be genetic, stress, inflammation, infections, toxins, alcohol, using cocaine, air pollution, autoimmune diseases, and the emotional state of the child and caused by environmental factors during pregnancy and the first 2 years after the birth.[5] Some studies on monozygotic and dizygotic twins have been completed to effectively investigate the genetic factors that caused ASD. According to studies, the concordance rate of monozygotic twins was higher than the concordance rate of dizygotic twins. However, the concordance rate of monozygotic twins was not %100. This case demonstrated that ASD is caused by more than just genes.[6,7]

Stress is one of the most important environmental factors. Prenatal stress is still being studied, and the severity, duration, and type of stress are also all up for discussion. However, some research shows that ASD is associated with prenatal stress. Also, it has been observed that prenatal stress has similar symptoms to ASD with animals. According to the study conducted on Rhesus monkeys by Coe et al.,[8] if the mother is exposed to stress hormones during the prenatal period, changes in the kid monkey's immune system occur after birth. Therefore, it can be suggested that prenatal stress may increase ASD risks which is occured with viral and bacterial infections.[9]

The inflammation that occurs in the brain, may affect neurons and damage some parts of the brain and may prevent the connection of neurons. In addition, this may cause ASD.[10] Autism can

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be caused by inflammation not only in the brain and nerve cells, but also in other parts of the body. For instance, according to the study by Erbaş et al.,[11] it was shown that giving fructose to rat pups for an extended period of time caused fatty liver. Inflammation was triggered by fatty liver and metabolic syndrome. Neurobehavioral effects on offspring have been observed as a result of this investigation, which have been associated with maternal metabolic syndrome-related inflammation. Infections during pregnancy can damage the fetal brain with some viruses like prenatal influenza, rubella, cytomegalovirus. This damage might result in ASD.[12,13] Externally obtained toxins from maternal health are risk factors for ASD. These toxins may directly affect the brain, or they might change the methylation pattern of autism-associated genes.[14]

ASD symptoms appear gradually during the first six months and are noticeable by age three. Poor social skills, communication difficulties, and repeated tendencies are some of the signs.[15]Autistic people have some social impairments. Their sense of empathy is weak. Abnormality in their social aspects becomes obvious in early childhood. They are less responsive to social stimuli. They do not react when someone calls them. Also, they have trouble with making eye contact.[16] Making friends is also diffcult for them. It's a common misconception that autistic people don't want to make friends, but this isn't accurate. Autistic kids are more likely than their peer to feel loneliness. For them, the quality of friendship is more important than the number of their friends.[17] Their conservations usually take the form of a monologue, in which only they speak. They might mix syllables or words while talking. Also, they might have difficulty when they want to tell something or convey their feelings.[18,19] Autistic people can continue the same behaviors, what they are obsessed with. They are passionate about participating in anxiety-relieving actions. For instance, they often wash their hands for cleanliness or kids consistently desire the same clothes regardless of the weather.[20] Watching the same TV show or playing with the same toys are two examples of repetitive habits. Furthermore, they may study a subject down to the tiniest detail, but they only learn that subject.[21]

Autistic individuals may show other symptoms independent of diagnosis. Emotional abnormalities are also found in people with autism. They have a habit of choosing food because they are obsessed.[22]

The research by Fombonne[23] showed that autism is more common in men. The ratio of men to women is 4,3 to 1. Therefore, men are in the high-risk group compared to women. This rate can change depending on cognitive impairment. The rate is 5,5/1 in situations where cognitive impairment is not seen, and 2/1 in cases where cognitive impairment is not observed. The reports on the relationship between maternal age and ASD are conflicting. Some studies suggest that there is no correlation, others claim that maternal age raises the incidence of autism.[24]

There are two types of treatment for ASD: education and medication. Other alternative medicine research exists, however these are not scientifically proven approaches. Education methods do not aim to treat it. Autistic people are guided to science, art, and other subjects through various educational approaches. In this way, their intellectual performance is improved. Methods such as applied behavior analysis, developmental models, speech therapy, and social skill therapy are commonly used.[25]

When education methods fail, medication is applied. Antidepressants, stimulants, and psychotics are the most common drugs. These drugs aim to curb aggressive and self-destructive behaviors. On the other hand, these drugs may have some side effects like weight gain and tiredness.[26] These methods of treatment, unfortunately, do not contain definitive results. It aims to bring autistic individuals into society and reduce the distress suffered by the family.[27]

CHOLESTEROL

Cholesterol is an organic molecule that is essential for cell membranes. It is a sterol that is carried in blood plasma. It is a component of animal cell membranes and makes cell membranes gain flexibility. All animal cells synthesize cholesterol. Also, some plants produce a small amount of cholesterol, but prokaryotes do not produce it. A considerable amount of cholesterol exists in tissues and organs with a great number of membranes.[3]

The chemical formula of cholesterol is C27H46O. Cholesterol has 8 stereocenters.[28] Besides the cyclic carbon chains, there is also a hydroxyl group in the structure of cholesterol. This hydroxyl group makes cholesterol an alcohol. The hydrophilic property of cholesterol is provided by the hydroxyl group, whereas the hydrophobic property is

contributed by the cyclic portion.[29] Cholesterol is usually found in esterified form in plasma and loses its hydroxyl group to transform into an esterified form. Therefore, esterified cholesterol does not have hydrophilic property.[30]

Cholesterol is used for the biosynthesis of steroid hormones, bile acid, and vitamin D. This suggests that cholesterol is a precursor to these compounds. Also, it participates in many biochemical reactions. It may cause some disorders when cholesterol exists in blood plasma more than its optimum amount. It may accumulate in blood vessels and cause atherosclerosis. It can also create gallstones when it mixes with bile pigments.[3]

Cholesterol allows cell membranes to become more flexible and resistant to damage. It makes the cell membrane protected through interacting water with its hydroxyl group as the polar part of the cell membrane. It helps to produce lipid rafts in the membrane. Also, it acts in neural conduction and makes it faster. A myelin sheath, which is rich in cholesterol, provides isolation for impulses.[31]

It is the precursor molecule for vitamin D, all steroid hormones (adrenal gland hormones, cortisol, and aldosterone), and the sex hormones. It is recycled by the body and is secreted by the liver into the gallbladder and is stored there. The gallbladder empties it into the digestive system through bile. The small intestine reabsorbs %50 of it into the bloodstream.[32] Because the blood-brain barrier prevents lipoprotein from entering the brain, the brain produces its own cholesterol. Cholesterol synthesis begins with the conversion of acetyl-CoA to acetoacetyl-CoA. After this process, acetoacetyl-CoA merges with another acetyl-CoA and as a result of this, an HMG-CoA (3-hydroxy-3-methylglutaryl-CoA) molecule is formed. HMG-CoA converts to Mevalonate through the enzyme HMG-CoA reductase. This stage is considered an irreversible step and is a speed limiter for cholesterol synthesis. These steps are then followed by enzymatic reactions that convert mevalonate to Farnesyl-PP, Squalane, and Lanosterol respectively. Finally, cholesterol is obtained as a result of another 19-step process.[33]

However, if the amount suddenly rises or falls, it can cause problems. There are various processes in the body that prevent this from happening. Cholesterol is insoluble in water, and some molecules are used for carrying cholesterol. These are low-density lipoprotein (LDL) and high-density lipoprotein (HDL). LDL carries cholesterol to tissues from the liver. If its amount is so high in the bloodstream, it may accumulate in vessels and cause atherosclerosis. That is why LDL cholesterol is referred to as "bad cholesterol." HDL carries excess cholesterol to the liver to eliminate it, and it is called “good cholesterol”.[34]

It is also produced in great amounts by the liver and small intestine. The bile transports cholesterol from the liver to the small intestine. It is absorbed in the small intestine and passes into the bloodstream. So the only cells in the body capable of removing cholesterol are situated in the liver, HDL transports cholesterol from the tissues to the liver. Cholesterol is excreted from the liver through bile and most of them are absorbed back.[35,36] The most commonly used way to decrease LDL level is using statins. Statins are a class of lipid-lowering medications. They are used to reduce the risk for cardiovascular disease. Statins, like any medicines, have some side effects. Muscle pain, increased risk of diabetes mellitus, and abnormal blood levels of liver enzymes are some of them. Diet is another factor that affects cholesterol levels. Cholesterol is prevalent throughout the body, particularly in the liver. That means eating liver or animal food increases the level of cholesterol in the body. Consequently, eating foods that contain less cholesterol may help to decrease cholesterol levels in the body. This may help people who are in the high-risk group for cardiovascular disease.[37-40]

AUTISM AND CHOLESTEROL

The brain contains one-quarter of all cholesterol in the body. That means cholesterol has a big effect on the brain.[41] In this way, cholesterol may affect autism. It occurs with impaired brain development.[42] As a result, ASD may occur if neurons are harmed or destroyed.[43] It has an important role in neuron development because it is found in cell membranes, thus it is important for neurons and synapses.[44] Oligodendrocyte cells are found in the nerve system, and they are a type of glial cells. They are responsible for the production of myelin sheath for neurons that are found in the central nervous system. And oligodendrocytes need a high amount of cholesterol to produce myelin sheath. So high cholesterol is essential for myelin sheaths.[45] Therefore, cholesterol deficiency may cause structural disorders in neurons, and it may lead to autism. Cholesterol may have some degenerative effects.[46] Loss of cholesterol from plasma membranes causes loss of lipid-rafts,

and it may lead to impaired neurotransmitter release. This occurrence is associated with neurodegeneration and demonstrates cholesterol's neurodegenerative effect.[47] In addition, cholesterol can not cross the blood-brain barrier, and it may accumulate in the central nervous system. Cholesterol affects the nerve nodes and makes neuron cells change their structure when it accumulates too much. This situation may cause ASD.[48,49] Thirumangalakudi et al. found neuroinflammation in hypercholesterolemic mice in a mouse study. This neuroinflammation may directly cause ASD. Besides, local immune cells that accumulate around the area of the brain inflammation may cause neurodegeneration and synaptic/cognitive dysfunctions and these dysfunctions may result in ASD.[50] They mentioned that even the slightest inflammation may affect neural development. Due to the high cholesterol level, the body may create inflammation against cholesterol.[51] Even the body's own inflammation has been connected to ASD.

AUTISM AND LIPID METABOLISM

Researches show that autistic people's lipid and cholesterol levels differ from normal values. Researchers examined whether autism and lipid metabolism are connected. They have detected that autistic people had different amounts of bad cholesterol (LDL), good cholesterol (HDL), and triglyceride levels. Their lipid levels were higher than normal values.[52]

They also discovered that autistic people's abnormal lipid metabolism rate is twice as high as non-autistic people's abnormal lipid metabolism rate. Furthermore, there is a familial correlation. Mothers who have an abnormal lipid metabolism are %16 more likely to have a child with autism than mothers who do not have an abnormal lipid metabolism. This rate is %13 for fathers. And an autistic child is %76 more likely to have an abnormal lipid metabolism than their siblings.[53] According to the study, epilepsy, sleep difficulties, intellectual incapacity, and anxiety are all associated with ASD and low cholesterol levels. The rate of showing these symptoms is higher for people who have both ASD and low cholesterol levels than people who have just autism.[52,53] Also, people with autism and abnormal lipid metabolism have a high risk for anemia, hypothyroidism, and vitamin D deficiency.[53] They recently found relation shows that patients with Rett Syndrome, which is correlated to ASD, have a mutation in a gene involved in cholesterol metabolism. This link also showed that between 50 and 88 percent of children born with Smith-Lemli-Opitz syndrome, due to a disorder in cholesterol synthesis, had ASD.[53]

Conclusion

ASD is a disease caused by disorders in the brain and neurons. As a result, cholesterol has a significant impact on ASD. Any disorder in cholesterol metabolism may cause ASD and this type of this may be treated with the correction of cholesterol metabolism. The main point is whether the person with this disorder has an impaired cholesterol metabolism. If the disorder is related to cholesterol, correcting cholesterol metabolism may be able to treat it. These findings are crucial because they demonstrate a link between ASD and cholesterol, which is excellent sign for many autistic people.

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