

Role of Serum Cholesterol Level in Pathogenesis of OCD

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Abstract

Etiology and pathophysiology of obsessive compulsive disorder remains inconclusive till today. Multiple converging lines of evidence suggest that neurobiology plays a significant role in the etiology of obsessive compulsive disorder (OCD). Certain brain areas frequently involved in symptomatology of OCD, analyzed by neuroimaging studies. The strongest pharmacologic evidence concerns the serotonergic system and the well-established efficacy of potent serotonin reuptake inhibitors in the treatment of OCD. Cholesterol forming the vital component of neurons regulates neurochemical activity. Reduced serum cholesterol level causes hyperactivity of serotonin reuptake receptor activity precipitating symptoms of OCD.

Keywords: OCD; Serotonin; Receptors; Neurotransmitters; Cholesterol

Introduction

Obsessions are recurrent, persistent, thoughts, images or impulses that are experienced as intrusive & inappropriate [1].

Compulsions are repetitive behaviors or mental acts that the person feels driven to perform in response to an obsession or according to rigid rules [1].

Obsessive-compulsive disorder is the fourth commonest psychiatric disorder with disability in severe cases often comparable to the disability associated with mental illness such as schizophrenia and bipolar disorder. 2% of adults suffer from this disorder [2,3].

The OCD usually presents at the age of 20-30 yr. If it presents in older age (in 4th decade) it usually comes after a stressful situation in life. OCD usually begins in adolescence or early adulthood although it can begin in childhood. Nearly 65% of the patients have the onset before 25 years of age and <15% have onset after 35 years of age [2,3].

Epidemiological studies show that around 2% of adults suffer from this disorder.

Etiology [3,4]

Neurobiological factors

Onset of OCD symptoms follow neurological injury secondary to infection, head injury or neuronal over activity.

Efficacy of serotonin reuptake inhibitors in symptomatic improvement in OCD cases has proved role of serotonin in pathophysiology of OCD.

Neurophysiological factors

Positron emission tomography (PET) studies suggest increased glucose metabolism in orbital frontal cortex, pre-frontal cortex and anterior cingulate gyrus, right caudate nucleus.

Neuroanatomical factors

Neuroimaging studies that have been implicated the frontal-basal ganglio thalamic cortical circuit in the pathogenesis of the disorder.

Neurochemical basis

Oxidative stress causes neuronal damage in the above mentioned areas. Damage caused disturbs intracellular events resulting in impaired release of neurotransmitters like serotonin, dopamine which have been

proposed in the pathophysiological basis of OCD, thus decreasing the synaptic levels of neurotransmitters leading to symptomatology.

Neuropsychological factors

Immunological factors

Subgroup of youngster's present OCD symptoms triggered or symptoms get precipitated with group a beta hemolytic streptococcal infection

Family history

50% childhood cases are familial.

Genetic factors

Studies suggest that 30% of adults with OCD had immediate family member with symptoms of OCD. Research suggests that if one parent has OCD the chances of the child having it are between 2% and 8%.

Behavioral factors

According to Hobart Mowrer's conditioning theory, previously neutral stimulus becomes aversive, as a result of being associated with an unrelated aversive stimulus

Compulsions become strengthened as a result of anxiety reducing properties.

Types of OCD

There are five main types of OCD that commonly appear in sufferers [6,7].

Washers and cleaners

Contamination obsessions are the most common type of obsessions in OCD. They are typically characterized by a fear of dirt or germs.

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Obsession: a constant fear of contamination and being infected with disease and infecting others. Compulsion: sufferer avoids or removes all possible sources of germs and dirt. Washers may repeatedly wash their hands or take showers while cleaners may clean their house repeatedly.

The cleaning compulsions include excessive or ritualized hand washing, showering, bathing, tooth brushing, and elaborate toilet routines.

Checkers

Obsession: a fear of forgetting to lock or switch something off will cause harm for which they will be blamed. Compulsion: time consuming rituals that involve checking & re-checking the objects of their obsession for eg. Locks/ switches.

Patients with doubts typically worry that something terrible may happen because they have not completed an act thoroughly or completely. Such patients can spend hours checking before leaving their home.

Orderers

Obsession: To organize or arrange objects in a specific pattern or order before performing a daily task.

Compulsion: Arranging things in a certain 'correct' way. If someone else touches or moves those objects out of place, they will feel extremely upset.

Hoarders

Obsession: Excessive fear of discarding certain objects in the belief that they may be of use in the future.

Compulsion: Keeping or collecting items those are often useless. Even if some are useful, hoarders tend to collect so many items that they are unable to finish using all of them.

Sexual and aggressive obsessions

Patients with these obsessions are plagued by thoughts, images or urges that are sexual or aggressive in nature. Patients often fear that they may commit a sexually unacceptable act such as touching the private parts of immediate family members. Aggressive obsessions include fears that one might harm self or others on an impulse (fear of stabbing with a knife, jumping in front of a car, leaping out of an open window) or because not careful enough (fear of hitting a pedestrian because of not being careful), and fear of blurting out obscenities or insults [5,6].

Neurotransmitter involved in OCD pathophysiology

Serotonin is a monoamine neurotransmitter, biochemically derived from tryptophan. Primarily found in gastrointestinal tract, Central Nervous System, platelets etc. Functions of serotonin include the regulation of mood, appetite, sleep, cognitive functions, including memory and learning [8,9]. Serotonin is the major neurotransmitter in raphe nuclei, which are grouped into nine pairs and distributed along the brainstem, centered around the reticular formation. Axons of neurons in the "caudal" raphe nuclei terminate at deep cerebellar nuclei, cerebellar cortex, spinal cord. Serotonin is released at terminal synaptic boutons acting at a wide gap of >20 μm synapse and acts to activate 5-HT receptors located on the dendrites, cell bodies and presynaptic terminals of adjacent neurons. Serotonin receptors are G protein coupled seven transmembrane (or "heptahelical") receptors that activate an intracellular second messenger cascade except 5-HT₃, which is ligand gated ion channel [10].

SERT spans the plasma membrane 12 times. It belongs to NE, DA, SERT monoamine transporter family. Transporters are important sites for agents that treat psychiatric disorders. Both drugs that reduce the binding of serotonin to transporters (selective serotonin reuptake inhibitors, or SSRIs) and, less often, that increase it (selective serotonin reuptake enhancers, or SSREs) are used to treat mental disorders. About half of patients with OCD are treated with SSRIs. Fluoxetine is an example of a selective serotonin reuptake inhibitor, and tianeptine is an example of a selective serotonin reuptake enhancer. The highly evolutionarily conserved serotonin transporter (SERT) regulates the entire serotonergic system and its receptors via modulation of extracellular fluid serotonin concentrations [11].

Cholesterol and OCD

Cholesterol is the vital component of eukaryotic cell membranes and plays a crucial role maintaining cellular function, membrane dynamics, transport across cell membranes and physical protection. The alteration in membrane physical properties is due to interaction of cholesterol moiety with various protein components in cellular membranes.

The heterogeneity in cholesterol distribution in membrane domains sequester proteins contributing to significance membrane function. The seven transmembrane domain G-protein coupled receptors (GPCRs) are among the largest protein families in mammals and represent 2% of the total proteins coded by the human genome. They mediate transduction events, which are the primary means of cellular communication and response to external environment. The recently reported role of cholesterol in the function and organization of the neuronal serotonin 1A receptor, a representative of the GPCR family which is present endogenously in the hippocampal region of the brain, is highlighted. The neurotransmitter release at the synapses underlies fundamental brain activities such as cognition, emotion, and memory. It is therefore natural to speculate that the neurotransmitter release depends on the cholesterol level in the brain. A low cholesterol level may alter the pattern of the release, which in turn perturbs the brain activities to the extent that it could lead to behavioral dysfunction, depression, suicide, and memory loss [12].

Cholesterol in pre-synaptic terminals

There exists an elaborate assembly of protein and lipid components, releasing the transmitter from pre-synaptic neurons. Cholesterol is the vital component of exocytosis apparatus playing a crucial role in biogenesis and transport of neurotransmitters and other substances in synaptic vesicles.

Synaptosomal preparations are used to calculate the lipid composition of pre synaptic terminals. The cholesterol: phospholipid ratio lies between 0.5: 1 in plasma membranes. The inner leaflet of synaptic membranes contains eight-fold more cholesterol than its outer counterpart and that this distribution is affected by disease and aging. Syntaxin and SNAP25, which form the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex with vesicle-associated membrane protein (VAMP), but none of the other exocytosis relevant proteins tested partitioned to the detergent-insoluble cholesterol-rich membrane fraction [13-15].

Presynaptic transmitter release involves interplay of two highly specialized compartments, the membrane at the docking zone and the membrane of synaptic vesicles. The molecular composition of synaptic vesicles has been characterized, since these organelles can be purified to a high degree from synaptosomes due to their abundance and uniform size. Cholesterol has profound effects on the biophysical

properties of membranes, thereby affecting the function of membrane-resident signaling components including ion channels, transporters and receptors. In a molecular level, cholesterol can affect synaptic membrane fusion in a number of different ways:

cholesterol is proposed to form laterally separated membrane domains called rafts, in cooperation with another brain lipid sphingolipid. The rafts could play a role in driving the clustering of SNAREs into a specific membrane site, which may be necessary for productive fusion.

it is shown that cholesterol induces the clustering of the SNARE proteins by promoting self-assembly of the proteins without the rafts. The clustering of SNAREs is thought to be helpful for docking and fusion of vesicles.

due to its unique inverse wedge-like molecular shape, cholesterol is thought to play a role in membrane fusion which involved curving and bending of the bilayers [16].

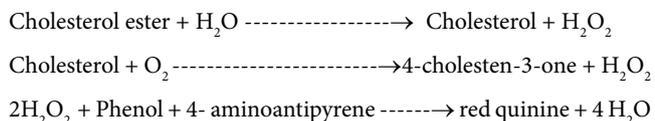
Estimation of Serum Cholesterol level

Method: cholesterol oxidase peroxidase methodology (Agappe diagnostics)

Sample collection: After taking informed consent, under thorough aseptic precautions, 2 ml of venous sample is collected from the patient in a plain vacutainer and allowed to clot. After one hour, the vacutainer is centrifuged at 2500 rpm for 5 min and serum is extracted and stored.

Principle of CHOD-POD method

Enzymatic colorimetric determination of total cholesterol according to the following reactions.



Reagent composition

Cholesterol Standard: 1 × 5 ML (Table 1)

Preparation and stability of working reagent: Dissolve contents of reagent 2 (R₂) with the amount of reagent 1 (R₁) indicated on the vial label. The working reagent is stable for 90 days at 2-8°C.

Wavelength for estimation: 505-630 nm

Linearity: 500 mg/dL

Procedure

	Blank	Standard	Sample
Working reagent	1000 µL	1000 µL	1000 µL
Standard	-	10 µL	-
Sample	-	-	10 µL

Mix and incubate for 5 min. at 37°C. Measure the absorbance of sample and standard against reagent blank.

Cholesterol R ₁ : 2 × 50 ml		Cholesterol R ₂ : 2 × 50 ml	
Pipes buffer (pH 6.9)	50 mmol/L	Cholesterol esterase	≥ 200 U/L
Phenol	24 mmol/L	Cholesterol oxidase	≥ 250 U/L
Sodium cholate	0.5 mmol/L	Peroxidase	≥ 1000 U/L
		4-aminoantipyrene	0.5 mmol/L

Table1: Cholesterol standard of concentration: 200 mg/dL.

	Cases	Controls
Mean age ± SD (years)	34.5 ± 9.26	34.03 ± 8.52
Sex	16 M/14 F	17 M/13 F

Table 2: Baseline characteristics of patients.

Calculation

Cholesterol concentration (mg/dL)=(Absorbance of sample / Absorbance of standard) x 200

Normal Range: 140 – 200 mg/ dLs

Method

This is a case control study on 30 cases and 30 control group with match of age, sex and inclusion /exclusion criteria. Selected age group is between 15-45 years. excluding the cases and controls with history of metabolic disorders, smoking, alcohol consumption, unwillingness in participation in study.

Results

All the calculations were done using Microsoft Office Excel 2010 and statistical analysis was done using the Graph Pad Prism software, version 5.01.

The collected data was analyzed by applying paired t test. P-value less than 0.05 (P<0.05) was considered to be statistically significant (S). P-value less than 0.001 (P<0.001) was considered to be statistically highly significant (HS). P-value more than 0.05 (P>0.05) was considered to be statistically non-significant (NS) (Table 2).

The average age of subjects in controls is 34.03 years and 34.5 years in patients with OCD, which shows that mean age is nearly equal in controls and cases.

Sex distribution in controls 17 males and 13 females and in patients with OCD 16 males and 14 females, which shows that sex ratio is nearly equal in controls and cases (Graph 1).

There is significant decrease in serum cholesterol in OCD cases as compared to controls since (p value 0.0047 i.e.<0.05) (Graph 2).

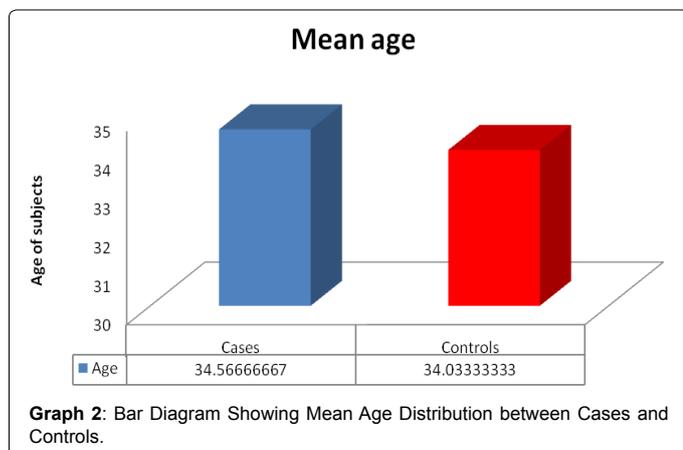
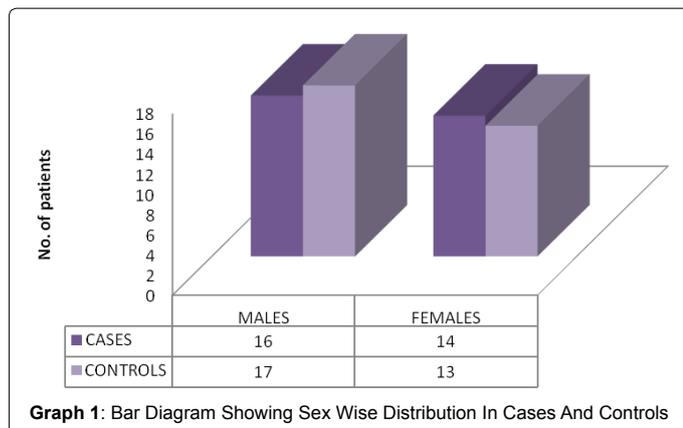
Discussion and Conclusion

Obsessive-compulsive disorder (OCD) is a neuropsychiatric disorder characterized by recurrent distressing thoughts and repetitive behaviors or mental rituals performed to reduce anxiety. Symptoms are often accompanied by feelings of shame and secrecy because patients realize the thoughts and behaviors are excessive or unreasonable. This secrecy, along with a lack of recognition of OCD symptoms by health care professionals, often leads to a long delay in diagnosis and treatment

Brain is highly enriched in cholesterol containing almost one quarter of total bodily cholesterol. In neurons, cholesterol makes up nearly 40% of total membrane lipids and is in equilibrium with serum cholesterol level. Lowered serum cholesterol levels as seen in cases with respect to controls causes reduced levels of neuronal membrane cholesterol, which cause impaired release of serotonin due to inefficient exocytosis and SERT dysfunction causing exaggerated uptake of serotonin from synapse. Thus there exists relative deficiency of serotonin in the synapses, which impairs neurotransmission leading to misfiring of neurons and misconveyed impulse transmission precipitating symptoms of OCD [9].

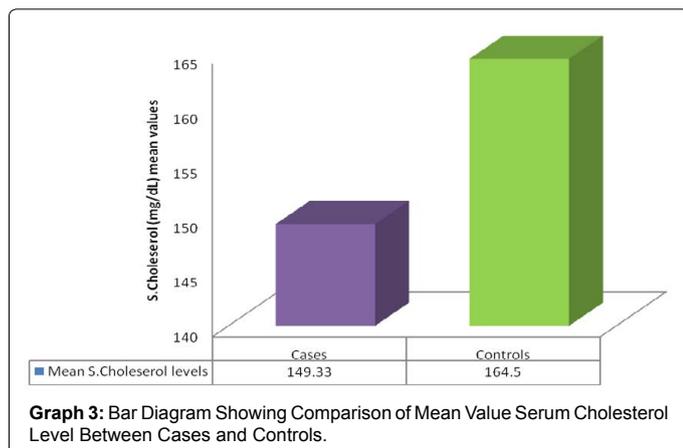
OCD and serum cholesterol level

➤ Cholesterol is an essential component of eukaryotic membranes



Group	S. cholesterol level (mg/dL) Mean ± SD	T value	p value
Cases	149.33 + 25.65	4.88	<0.05
Controls	164.5 + 16.95		

Table 3: Comparison of serum cholesterol level between cases and controls.



and plays a crucial role in membrane organization, dynamics and function. Cholesterol is a multifaceted molecule, which serves as essential membrane component, as cofactor for signaling molecules and as precursor for steroid hormones. Cholesterol plays a vital role in the activity of membrane transporter e.g SERT (serotonin transporter).

➤ Reduced Serum cholesterol levels in OCD patients also depict

low levels of neuronal membrane cholesterol and the increased activity of serotonin transporter (SERT), integral membrane protein which reuptakes serotonin from synapse leading to relative deficiency of serotonin in the synapse that inturn lead to symptoms of OCD.

➤ Lowered serum cholesterol levels causes impaired release of neurotransmitter serotonin because of inefficient exocytosis of pre-synaptic neuronal vesicles. And SERT activity is impaired resulting in faster and exaggerated serotonin uptake. Thus the synapse becomes deficient in serotonin causing neuronal irritability and excessive transmission of impulses resulting in OCD symptoms.

➤ In the present stud y, there was significant decrease in serum cholesterol levels in cases (149.33 ± 25.65) (p<0.05) (Table 3 and Graph 3) as compared to the control group (164.5 ± 16.95) (p>0.05). This shows that the role of decreased serum cholesterol level in the pathogenesis of OCD

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