Review Article

The Pathophysiological Bases of Obsessive Compulsive Disorders

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Purpose of review

This review considers the neurobiological aspects and the genetics of the Obsessive-compulsive disorders (OCD). The recent advances in OCD research showed the increasing role of alteration in both the molecular and cellular mechanisms. These altered physiological mechanisms were clinically evident through phenomenology, neuropsychology, neuroimmunology, and neuro-imagery among the patients with OCD. The most consistent finding throughout the researches was the involvement of various cortical and subcortical regions, especially the orbitofrontal cortex (OFC), the anterior cingulate cortex (ACC), the dorsolateral prefrontal cortex (DLPC), the head of the caudate nucleus and the thalamus in the development of OCD. Neuropsychiatric genetic literatures have been expanded to highlight the genetic bases for the development of OCD and their role with various environmental conditions in determination of the disease prognosis and resistance to treatments. This review also discussed uncommon etiologies for OCD, like infections and traumatic brain injuries (TBI). These findings will provide new approaches for better diagnostic and treatment advances.

Introduction

OCD is characterized by the combination of intrusive thoughts and repetitive behaviors, which might impede psychosocial performance. OCD is now a separate diagnosis with its own chapter, "Obsessive-Compulsive and Related Disorders," in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) (1). Recent findings in the genetic and the neurobiology of OCD showed that both have a limited impact on the near future management of this disorder, but they have started to clarify the underlying etiology. These findings will point to the tremendous opportunities for a better understanding of the diagnosis and treatment of OCD.

Phenomenology, clinical course, and epidemiology

Table 1. shows that the main themes in the obsession and compulsions have different modalities.

The lifetime prevalence of the OCD is about 2.5%. The most common age to start symptoms of OCD is between 10-24 years. There is no gender-based variation among patients with OCD. The onset of symptoms in males tend to start in childhood and it is common with other tic disorder, while in female it is common in their twenties. OCD isn't uncommonly to start in pregnancy, and the symptoms usually get worse in premenstrual period and pregnancy for those females previously diagnosed with OCD. (1)

Discussion

Key Points

- Recent neurobiological studies highlighted the functional and the morphological of certain cortical and sub-cortical centers among patients with OCD. The roles of dopamine and 5HT neurotransmitters have been discussed.

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- OCD has been known to have a strong genetic basis. The review discussed some of the common and rare genetic variation among the patients with OCD.
- The neuropsychologic bases for OCD might play an important role to understand this disorder. The role of the cognitive and the behavioral aspects have been discussed.

Other less common associations with various physical illnesses were discussed in the context of this review, these supported by figure (1)

This model shows the role of neurobiology, genetics, and environmental factors involved in the etiology of OCD [(2)].

A. Neurobiological etiology

Normal behavior is the result of integrity of many cortical and sub-cortical centers, namely, the anterior cingulate cortex (ACC), the orbitofrontal cortex (OFC), the dorsolateral cortex (DLPC), the head of caudate nucleus, and thalamus. The function of the ACC is the involvement in conflicting situations and the possibility of mistakes, while the OFC is significant in decision-making process. The DLPC is the essential part in the cognitive process. The inputs of these cortical centers are coordinated and integrated in the caudate nucleus, which is responsible for the behavior. As shown in figure (2). Abnormalities in one or more of those centers result in the behavioral characteristic of OCD. [(3)]

This photo shows the main centers involved in the pathogenesis of OCD, namely, Anterior Cingulate Cortex (ACC), Prefrontal Cortex (PFC), and Prefrontal cortex (PFC). [(4)]

Table 1. Categories of the obsession and compulsions:

Obsessions	Associated Compulsions
Fear of contamination	Washing, cleaning
Need for symmetry, precise arranging	Ordering, arranging, balancing, straightening until "just right"
Unwanted sexual or aggressive thoughts or images	Checking, praying, "undoing" actions, asking for reassurance
Doubts (e.g., gas jets off, doors locked)	Repeated checking behaviors
Concerns about throwing away something valuable	Hoarding

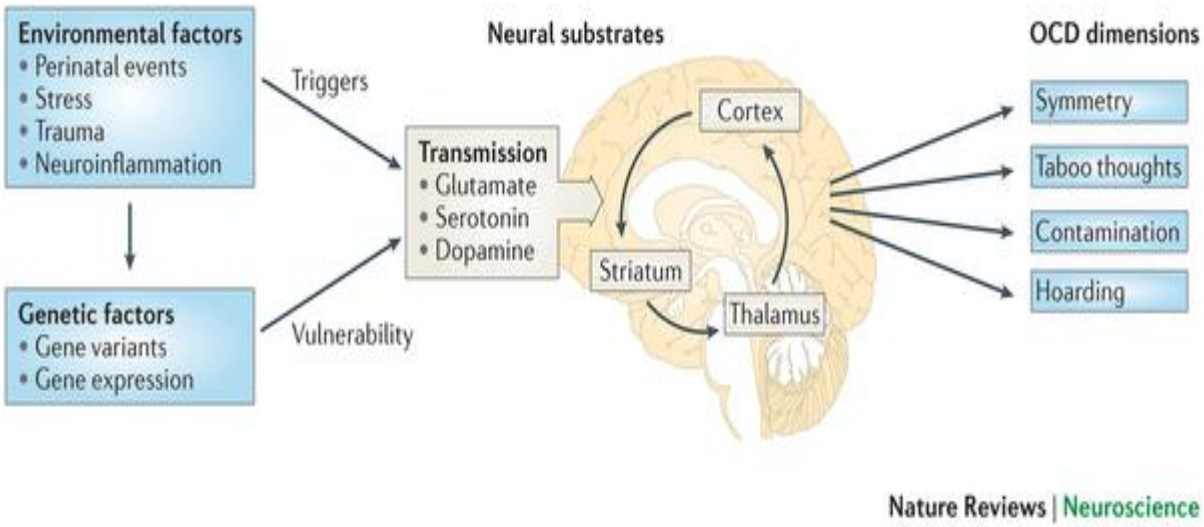

Figure 1. Etiology of OCD [(2)]

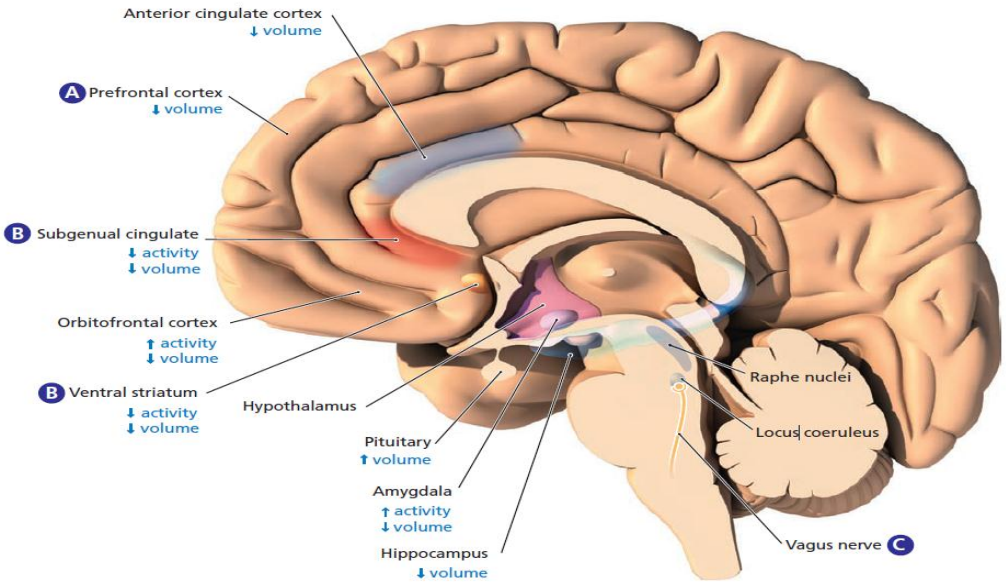

Figure 2. neuroanatomical bases of OCD [8]

The anterior cingulate cortex (ACC) consists of two parts: a ventral (affective) region, which is responsible for keeping attention on the internal emotional and motivational status and managing the autonomic responses; and dorsal (cognitive) region, which has many functions including attention, working memory, error detection, conflict monitoring, response selection, and anticipation of incoming information. The ventral striatum is closely connected to both OFC and ACC, which take part in the preparation, initiation and execution of reward-based behavioral responses after the cognitive and emotional integration of information at the cortical level. The functional imaging studies were associated with higher activity in the OFC, ACC, head of the caudate nucleus and thalamus in patients with OCD. These abnormal findings were observed in both basal and provocation states. It is also interesting to know that the treatment of the patient with OCD either by SSRI or CBT resulted in the reduction in the activity of ACC, OFC, and caudate nucleus. These findings are highlighting the association of 5HT neurotransmission with the abnormal activity of the frontal-subcortical loops (OFC and ACC). Other research findings stated that the dopamine system, with which 5HT interacts, might have a significant role in the etiology of OCD. [5]

The functional neuroimaging showed that not only the cortico-striato-thalamo-cortical feedback loops were affected, but also other parts of the brain, such as the inferior parietal lobe, the anterior and posterior cingulate gyrus, insula, amygdala, cerebellum, have been affected. They also suggested that most important subtypes of OCD ("washing/contamination fear", "obsessions/checking", "symmetry/ordering", "hoarding") are involving various brain regions with partial overlap. Stimulation paradigms in fMRI-research are commonly based on symptom provocation by visual or tactile stimuli, or on action-monitoring and error-monitoring tasks. Deficits in action-monitoring and planning are discussed to be one of the basic dysfunctions of OCD. After psychotherapy and fMRI in patients with OCD, as shown in figure (3), there were significant changes in the activity of various brain regions, while the using of tactile and visual stimulations resulted in the exacerbation of the symptoms and alteration in the activity of many related brain areas. [6]

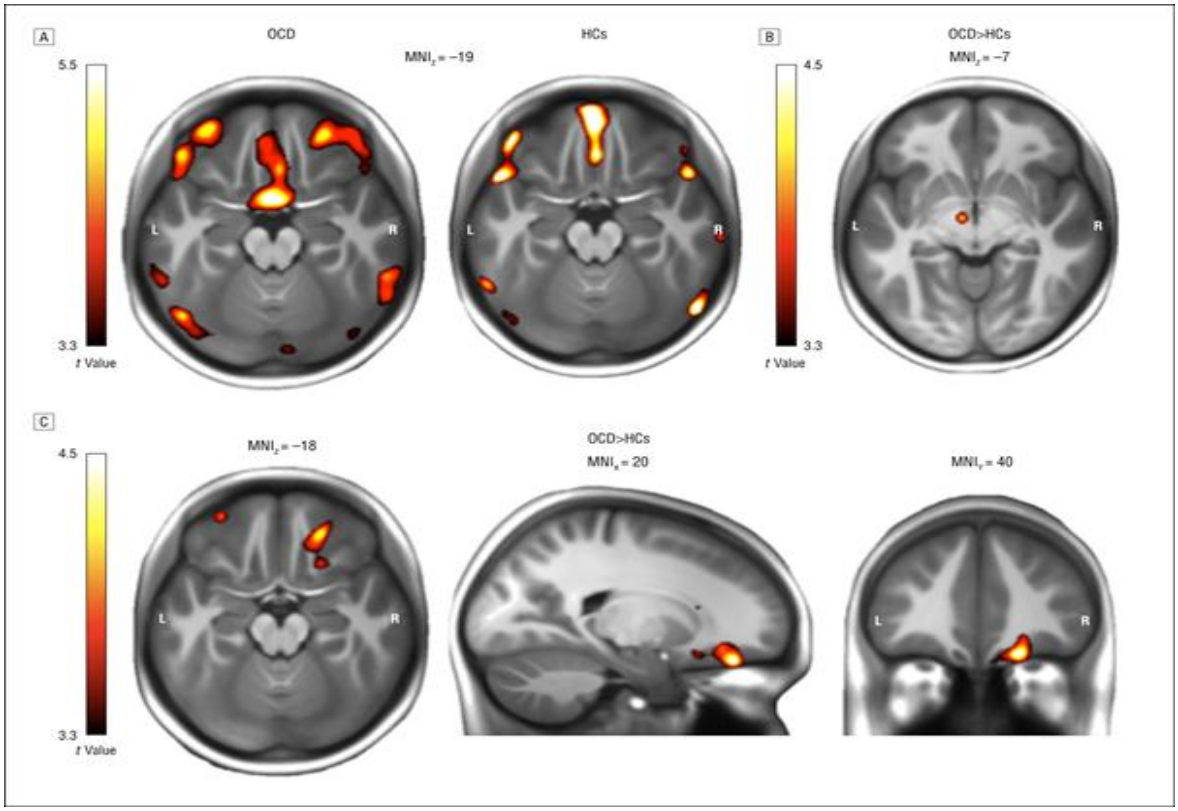

Figure 3. OCD versus control cases with fMRI [6]

Distant degree connectivity effects. A: Main effects in the orbitofrontal cortex (OFC) displayed for unmedicated patients with obsessive-compulsive disorder (OCD) and matched healthy controls. B and C: Greater degree of connectivity in the subthalamic nucleus and in the orbitofrontal cortex, respectively, in unmedicated patients compared with healthy controls. [7]

In addition to the findings of the circuitry dysfunctions of the fronto-striato-thalamocortical regions, there are increasing evidence about another circuitry dysfunction in the dorsolateral prefrontal cortex and parietal regions. This led to the suggestion that OCD represents the state of circuitry imbalance between the ventral and dorsal regions. [8]

The altered OCD-related activity in the pre-frontal cortex (PFC) has been noticed during the exacerbation of the OCD symptoms. They also predict the severity of illness and the degree of response to treatment. OCD-linked patterns of activity in these PFC regions are accentuated during provocation of symptoms and can predict treatment response; they tend to normalize following successful treatment. The use of high frequency stimulation (HFS) for the ventral internal capsule (VC)/ ventral striatum (VS) through the using of deep brain stimulation (DBS) would reduce the orbitofrontal cortex (OFC) activity, increase the delta band activity in OFC, and improve the degree of harmony within the PFC circuit. [9]

OCD is considered as one of the most common associated morbidity with the Gilles de la Tourette syndrome (GTS), which is characterized by multiple motor and one or more vocal/phonic tics. The underlying etiology for GTS is still unclear, but the possibilities of infections, pre-and para natal complications, neuro-immunological factors, and androgen effects might be involved in the pathogenesis. There is increasing evidence

about the abnormal neuroanatomical findings encountered among the GTS patients, mainly the cortical thinning and a reduction of the caudate nucleus size. [10]

The magnetic resonance spectroscopy for patients with OCD showed there was a significant alteration in the glutamate concentrations in both caudate and anterior cingulate cortex in patients with OCD. There is also an intimate relationship between the variant of glutamate system genes (SLC1A1) and the development of OCD in several studies. The strong evidence for the role of glutamate in the etiology of OCD found the base for the development of glutamatergic compounds (riluzole and memantine). [11]

There is increasing evidence about the involvement of the dopaminergic system in the etiology of OCD. Catecholamine-O-methyl-transferase (COMT) is considered as the main modulator in the neurotransmission of both noradrenergic and dopaminergic systems. The most common polymorphism of COMT gene had been associated with the increased its enzymatic activity by three to four times. This explained why the COMT been an interesting topic for many studies about its association with the development of OCD. The meta-analysis and literatures reviewing had shown that there is no significant association between COMT gene polymorphism and the OCD occurrence. [12]

The comparison between the resting functional activity data obtained for the 27 OCD patients and 66 normal controls by using recent data-driven global brain connectivity (GBC) for the whole brain and the prefrontal cortex (PFC). The analysis of the data showed that there were spots of reduced connectivity in the left lateral PFC. Also, there was an increased GBC activity in the left cerebellar cortex and right putamen. There was an increased activity of the GBC in the anterior thalamus and dorsal striatum, which have been reduced in activity in response psychotropic medications. Despite of the reduced connectivity of the ventral striatum/nucleus accumbens, there was an increased connectivity throughout the ventral anterior cingulate cortex among the patients with OCD. [13]

B. Neuropsychological (cognitive and behavioral) etiologies

Many studies have highlighted the significance of both the inhibition and the cognitive flexibility as underlying factors in the development of OCD, where the lack of inhibition and altered cognitive flexibility might explain the symptoms in various forms of OCD. The use of an attention model designed by Norman, Shallice, and Burgess described three integrating systems: the first one for the routine actions; the second one is controlling over the first one to stop the automatic process and activities to achieve the desired attention; while the third one is the cognitive control which takes control over the first and second parts when they fail in their function. The functions of the cognitive control are to identify any cognitive errors and analyze ambiguous events. The researches of neuro-cognitive function had detected the Cingular anterior cortex and the prefrontal lateral cortex to be involved in the ambiguous and confusing events. These two areas were considered as the main areas for inhibition of the routine actions and for the behavioral flexibility. The result would be an appearance of the repetitive rituals due the dominance of the system that control the automatic activities. There is also a Posner model of attention for OCD. It stated that mental inhibition has the required potential to deal with the information by two mechanisms: the first one is by not remembering the upsetting events; the second one is the automatic control over the events through inability of having emotions for certain events. This theory is describing the efforts to resist the intrusive thought as controlled and willful activity against any emotionally challenging input. In patients with OCD, the controlled efforts to repress obsessions stressful events might result in the emerging of intrusive thoughts, which

represents failure of the controlled treatment of information. The abnormal functional neuro-imagery findings are proposing the involvement of sub-cortical-frontal region in the development of OCD symptoms. They showed significant alteration and reduction in cognitive functions, due to lack of the adequate level of attention needed to regulate motor and cognitive activity. (14)

OCD might represent a dysfunction in the appraisal process, with subsequent development of the emotion of disgust. Disgust sensitivity is closely related to OCD and would predict the fear of contamination. The functional neuroimaging findings in the OCD patients (especially for contamination subtype) is closely related to the findings in disgust reactions, which involves the activation of the same neural parts in both situations. This suggests that both these reactions have the same neurocircuits. (15)

It was proposed that different regions of the brain are responsible for certain function, where the orbitofrontal cortex in involved in rewarding, the anterior cingulate cortex in the process of error revelation, the basal ganglia will affect the threshold for activation of motor and behavioral programs, and finally, the prefrontal cortex function is storing memories of behavioral sequences, called structured event complexes (SECs). The authors propose that the starting of the SECs may trigger anxiety that is relieved with completion of the SEC, and any dysfunction in this process might lead to the development of OCD symptoms. (16)

C. Genetic etiologies

During the study of the frequency of polymorphism in the coding areas of COMT genes, the sample was family-based. Fifty-six patient with OCD with their parents (control) were selected, and the genotype of the participants were analyzed. There was a significant association the frequency of low activity COMT allele and the female OCD patients (P=0.049), which was not seen in male patients. This finding suggest the role of COMT in the pathogenesis of OCD on gender-based pattern. (17)

In another study, it was designed to assess the gender-based difference among the OCD patients. Among the selected 220 patients, 107 were male and 113 were female. The patient underwent genotyping for polymorphism in MAO genes. The results of the study showed that the male patients with OCD have an earlier onset of the disease, worse future prognosis, and have distinct symptoms and axis I comorbidity. There was race-based variation in the gene polymorphism, where the Caucasians patients showed higher activity T allele of the EcoRV variant of the monoamine oxidase A (MAO-A) gene compared to controls. The African patients had more frequency of homozygous for the C allele at the G861C variant of the 5HT (1D beta) gene than controls. The Caucasian patients were more frequently homozygous for the low activity C allele of the EcoRV variant of the MAO-A gene compared to controls, with this allele also more frequent in female patients than controls. The other interesting finding in the study was that the female patients with OCD had more incidents of sexual abuse during their childhood, with the exacerbation of OCD symptoms in the premenstrual/menstrual period, after pregnancy, and during menopause. (18)

The interaction between the environmental factors and genetic susceptibility to OCD at the beginning of the clinical illness will determine the degree of pharmaceutical resistance among the patients. The study that included 238 patients with OCD, centered on the impact of interaction between the SLC1A1 gene variant and the level of life stress at the onset of OCD symptoms on the later development of pharmaceutical treatment resistance in OCD. The association of SNP (rs3087879), a copy of allele had been associated with significantly higher resistant OCD cases. This highlights the role of glutamatergic receptor system in determination of the

development and the prognosis of the OCD. (19)

The neuronal glutamate transporter gene (SLC1A1/EAAC1) had been shown to have significant association with the development of OCD, especially in males. The study screened 184 patients with OCD, and found that all of them have rare SLC1A1 amino acid variant. One variant of SLC1A1 missense, Thr164Ala, produced lower Vmax and Km activity in the transfected embryonic renal cells. It needs further investigation to study this effect on the brain circulatory function in the OCD. (20)

A study in Han, China on 206 OCD patients and 413 controls, had shown that there is no significant difference in the genetic polymorphism of the rs1805502, rs1805476 and rs890 in the 3'-UTR of GRIN2B among the controls and patients with OCD. (21)

It is not uncommon for schizophrenic patients who had been treated by second-generation antipsychotics (SGA) to develop the symptoms of OCD. This phenomenon was attributed to the presence of the three-single nucleotide polymorphism in SLC1A1 (rs2228622, rs3780412 and rs3780413), which encodes for the neuronal glutamate transporter excitatory amino acid carrier 1. The study recruited 103 schizophrenic patients who had the related genetic polymorphism, and were treated with SGA (anti-serotonergic); Clozapine showed more prevalence of the OCD symptoms ($P<0.001$). The severity of symptoms was related to the duration and dosage of the SGA. It is interesting to mention that there was no genetic association among the Asian patients with OCD. (22)

Studies showed that mice who are experimentally lacking the gene responsible for the coding of tryptophan hydroxylase 2 (Tph2) are showing various forms of behavioral disinhibition. Tph2 is a rate-limiting enzyme in the production of serotonin (5HT). The mice had significant impulsive and compulsive behaviors. The resultant impulsive behavior was motor one and not cognitive, where the mice kept reversal learning and normal acquisition. The treatment of these mice with 5HT resulted in improvement in their behavior. It is interesting to notice that the lack of 5HT was not associated with anxiety behaviors. (23)

It was found that, the association of the gene SLC6A4 and the OCD have been well documented. The current study recruited 572 normal Chinese college students to study the gender-related effects of the SLC6A4 on the development of OCD. During genotyping, seven tag SNPs and two functional tandem repeat polymorphisms (5-HTTLPR and STin2), that cover the entire SLC6A4 gene. It was noticed that males had higher OCS scores as compared with female students. The 5-HTTLPR in the promoter region showed the female-related genetic effects, where females with the both l/l and l/s genotypes have higher OCS scores than the s/s genotype. While, the males with SNPs (rs1042173| rs4325622| rs3794808| rs140701| rs4583306| rs2020942) of the SLC6A4 gene showed male-specific genetic effects, with the CGAAGG/CGAAGG genotype associated with lower OCS scores than the other genotypes. (24)

Variation in the mid-sagittal area of the corpus callosum (MSACC) was associated with different types of cognitive and behavioral disorders, like OCD, bipolar disorder, schizophrenia, ADHD, and autism. There is no strong evidence to suggest that MSACC is determined by certain heritable traits in the human beings, but in study of rats there is a little evidence about the genetic bases for this variation.(25)

The study of 33 Caucasian families from the US with the history of early onset of OCD. The genotyping studies showed that there are loci on chromosomes 1p36, 2p14, 5q13, 6p25, and 10p13. The most obvious result was on chromosome 1p36.33-p36.32. At this location, several of the families

showed haplotypes co-segregating with OCD. [26]

Another study recruited 225 patients with OCD and 279 controls. The study found that there was no significant variation in the frequency of genotypes among the OCD patients and the controls. It also showed that the rs1805476 single nucleotide polymorphism (SNP) is predominant among the male patients, while the four SNP (rs1805476, rs1805501, rs1805502 and rs1805477) were associated with the presence of contamination/cleaning symptoms. [27]

There was no significant association between the frequency of the dopamine D2 receptors (DRD2) Taql A and COMT Val (158) Met genotypes among the patients with OCD treated by combination of citalopram and quetiapine. The Met/Met genotype of the COMT receptors has a significant association (48%) among the responders to the 10 weeks' treatment combination of citalopram and placebo as compared to the non-responders. [28]

D. Various etiologies

The neuropsychiatric disorders following traumatic brain injury (TBI) are considered as a significant reason for TBI morbidity. The studies had shown that the TBI-induced psychopathology, mainly OCD, was largely affected by the presence of sub-clinical disorder, brain anatomical involvement, the surrounding level of stress, and the effectiveness of rehabilitation programs. The psychiatric interviews and the newly developed brain imaging studies would be used as a predictive parameter for the future neuropsychiatric morbidity after TBI. [29]

There are reports about the development of OCD symptoms, with or without tics, in both children and adults after acute infection with group A streptococcus. The exact pathophysiological changes were poorly understood, but the CNS autoimmune reaction is thought to be the underlying etiology, as in pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). Significant numbers of the patients had improved after completing the treatment with antibiotics. The symptoms of OCD would get worse with stress, but stress itself has no causative relationship with OCD. It is interesting to know that ways of parenting have no etiological relation with OCD. [30]

Conclusion

Recent advances in the genetics and neurobiology of OCD have focused the attention on specific cortical- striatal circuits and dopaminergic neurotransmission. The studies have shown specific alteration in the morphological and functional properties of the orbitofrontal cortex (OFC), the anterior cingulate cortex (ACC), the dorsolateral prefrontal cortex (DLPC), the head of the caudate nucleus and the thalamus. They also showed the possible underlying genetic risk factors, and the possible role of the dopaminergic and other neurotransmitter in the development of OCD. Large-scale studies are required to establish the relationship between the proposed pathophysiological findings and both related clinical patterns and treatment of the OCD.

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