Progress in Neuro-Psychopharmacology & Biological Psychiatry 70 (2016) 127–133

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Treatment-refractory obsessive compulsive disorder

Murad Atmaca *

Firat University, School of Medicine, Department of Psychiatry, Elazig, Turkey

ARTICLE INFO

Article history:
Received 2 September 2015
Received in revised form 4 December 2015
Accepted 9 December 2015
Available online 10 December 2015

Keywords:
OCD
Refractory
Treatment
Clinical aspects

ABSTRACT

Obsessive compulsive disorder (OCD) is a chronic and debilitating disorder. As can be seen in other psychiatric disorders, refractoriness to treatment is an important problem for patients with OCD. OCD is a chronic disorder like collagen tissue disorders, with symptoms tending to wax and wane but rarely remitting spontaneously through the course of the disorder. An important part of OCD patients respond to serotonin reuptake inhibitors alone or in combination with other medications, and cognitive behavior therapy. However, up to 30%–40% of patients do not respond to the available treatment modalities. The present paper tried to review the current state of knowledge on definition, clinical aspects, etiopathogenesis, and treatment strategies of patients with refractory OCD.

1. Introduction

Obsessive compulsive disorder (OCD) is a disorder which is classified under the category of Obsessive-Compulsive Disorder and Related Disorders in the Diagnostic and Manual of Mental Disorders Fifth Edition (DSM 5) (APA, 2013). As known well, the disorder has core symptoms of obsessions and compulsions. Obsessions are defined as intrusive unwanted thoughts, ideas, or images that are not simply excessive worries about real life problems and that are recognized as a product of the person's mind. On the other hand, compulsions are defined as repetitive behaviors or mental acts that the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly. According to data from the Epidemiological Catchment Area (ECA) survey and other epidemiological studies, the lifetime prevalence of OCD is between 2%–3% in the general population (Weissman et al., 1994). It has been reported that OCD is the fourth most frequent psychiatric disorder in the United States, with a lifetime prevalence of 2.5%, without any differences on ethnic backgrounds and populations (Karno et al., 1988). OCD shows a bimodal onset age, with peaks just before puberty period and fourth decade of life, with an equality of the ratio of male-to-female (Eichstedt and Arnold, 2001; Geller et al., 2001). OCD is a chronic disorder like collagen tissue disorders, with symptoms tending to wax and wane but rarely remitting spontaneously through the course of the disorder. An important part of OCD patients responds to serotonin reuptake inhibitors (SRIs) alone or in combination with other medications, and cognitive behavior therapy. However, up to 30%–40% of patients do not respond to the available treatment modalities (Saxena et al., 2001; Scarone et al., 1992; Robinson et al., 1995; Szeszko et al., 1999).

2. Clinical aspects

In fact, complete remission is a rare clinical condition in the course of the OCD. So, only a small part of the patients show complete resolution of the symptoms. In clinical practice, the implications "treatment-refractory" and "treatment-resistant" are often used for same meaning. However, there is an important difference between these terms. Treatment-resistant OCD has been described as the failure of at least two adequate therapeutic trials of SRIs (Goodman et al., 2000). Though debatable, the term treatment-refractory implicates a greater degree of resistance (Husted and Shapira, 2004). Husted and Shapiro described ones with treatment-refractory OCD as the patients who had failed at least three therapeutic trials of SRIs (with clomipramine being one of the SRI trials), the use of at least two atypical antipsychotics as augmentation strategies, and treatment with cognitive behavioral therapy while on a therapeutic dose of an SRI, with a demonstration of <25% reduction of Y-BOCS scores or, despite >25% reduction in Y-BOCS score, by still showing considerable impairment from their illness.

Abbreviations: OCD, obsessive compulsive disorder; ECA, Epidemiological Catchment Area; Y-BOCS, Yale-Brown Obsessive Compulsive Scale; OFC, orbito-frontal cortex; 5-HT, serotonin; OCD-D, pure OCD; OCD + D, OCD and depression; DST, dexamethasone suppression test; ACC, anterior cingulate cortex; SRIs, erotonin reuptake inhibitors; ERP, exposure and response prevention; FDA, Food and Drug Administration; CGI-SI, Clinical Global Impression-Severity of Illness and Improvement; NMDA, N-methyl-D-aspartate; CBT, cognitive behavioral therapy; TMS, transcranial magnetic stimulation; DLPFC, dorsolateral prefrontal cortex; DBS, deep brain stimulation; VNS, vagal nerve stimulation; ECT, electroconvulsive therapy.

* Firat (Euphrates) Universitesi, Firat Tip Merkezi, Psikiyatri Anabilim Dali, 23119 Elazig, Turkey.
E-mail address: matmaca_p@yahoo.com.

http://dx.doi.org/10.1016/j.pnpbp.2015.12.004
0278-5846/

3. Etiopathogenesis

Because of clinical heterogeneity of its clinical picture, etiology of OCD seems very complex. According to psychoanalytic theory, obsessions and compulsions reflect maladaptive responses to unconsciously unresolved conflicts from early periods of psychological development and in Freud's view the patient's mind responded maladaptively to conflicts between unacceptable, unconscious sexual or aggressive id impulses and the demands of conscience and reality. Our study group aimed to evaluate the relationship between the defense styles consisting of mature, immature and neurotic defenses and orbito-frontal cortex (OFC) volumes in the patients with OCD and thus, to take the first step interaction between psychodynamic and neuroanatomical dimensions of the disorder (Atmaca et al., 2011). We detected that there was no significant relationship between the right OFC volumes of both the patient and control groups and their scores of mature, neurotic, or immature defense mechanisms whereas the left OFC volumes were negatively correlated to the scores of immature but not mature and neurotic defense mechanism.

Genetic factors have been implicated in the occurrence of OCD. First of all, monozygotic twins have been found to be much more likely to show OCD symptoms compared to dizygotic twins (Grados et al., 2003). In addition, investigations of first-degree relatives have demonstrated that family members are at greater risk for OCD (Nicolini et al., 1991). The International OCD Foundation Genetics Collaborative (IOCDF-GC) performed a study to discover the genetic variation predisposing to OCD (Stewart et al., 2013. They reported that they did not find any single nucleotide polymorphisms (SNPs), but a significant enrichment of methylation QTLs and frontal lobe expression quantitative trait loci (eQTLs) were determined within the top-ranked SNPs (from the trio-case–control analysis), suggesting that these top signals might have a broad role in gene expression in the brain, and possibly in the etiology of OCD.

The role of serotonin (5-HT) has been well established in the pathogenesis of OCD. Among the 5-HT receptors, 5-HT_{2C} and 5-HT_{1D} receptors have been emphasized (Bergqvist et al., 1999; Koran et al., 2001; Stern et al., 1998; Mundo et al., 2000; Stein et al., 1999). On the other hand, dopamine is the other important neurotransmitter emphasized in the pathogenesis of OCD, with the finding that dopamine enhancers can increase obsessions, compulsions, and tics (Goodman et al., 1990), and with the support that dopamine antagonists such as atypical antipsychotics are beneficial agents for treatment-refractory OCD patients (Atmaca et al., 2002). SLC1A1, a candidate gene for OCD, was found to be associated with susceptibility to OCD, particularly in males (Arnold et al., 2006). In addition to neurochemicals of the brain, some neuroendocrinological markers have been examined in OCD. Our study group reported that reduced leptin levels might be related to patients with OCD and comorbid depression rather than pure OCD patients. Adiponectin was also examined by our study group (Atmaca et al., 2009) and was suggested that there might be an interaction between OCD and plasma adiponectin, with the proposal that one should keep into mind both the pathophysiologic dimension and cardiovascular vulnerability. Immunologic basis is another research area to account for etiopathogenesis of OCD. It has been reported that group A β-hemolytic streptococcal infections have been related to the onset and exacerbations of OCD (Leonard and Swedo, 2001). Our study team reported that glucocorticoids could lead to suppression of cell-mediated immunity and consequently could result in decreased neopterin levels in OCD patients (Kuloğlu et al., 2007).

Functional neuroimaging studies have showed that OCD patients may have a hyperactive brain circuit including the orbitofrontal cortex (OFC), anterior cingulate (ACC), thalamus, and striatum (Bjorgvinsson et al., 2007). Evidence for dysfunction in these regions has been also demonstrated in children with OCD (Brem et al., 2012).

Throughout the past two decades, structural neuroimaging studies have revealed important findings that contribute to the understanding of OCD pathogenesis, though neurobiological theories of OCD are largely based on the results of functional neuroimaging studies. However, in refractory OCD, it seems that there have not been enough investigations. Current knowledge from functional and structural neuroimaging emphasizes abnormalities of fronto-striatalthalamic-cortical circuits and orbitofronto-striato-thalamic circuits in the pathophysiology of OCD (Saxena et al., 1999, 2001). Welch demonstrated that mice with genetic deletion of SAP90/PSD95-associated protein 3 (Sapap3) exhibited increased anxiety and compulsive grooming behavior leading to facial hair loss and skin lesions; both behaviors were alleviated by a selective serotonin reuptake inhibitor, showing the critical role of SAPAP3 at cortico-striatal synapses and the importance of cortico-striatal circuitry in OCD-like behaviors (Welch et al., 2007). Among the regions of this circuit, some areas have been described as “key brain regions”, including OFC, thalamus, ACC and caudate nucleus. Our research team also performed a volumetric MRI study in treatment-naive patients and healthy controls, focusing on the *in vivo* neuroanatomy of these regions and demonstrated that OCD patients had significantly smaller left and right OFC volumes and significantly greater left and right thalamus volumes, compared with healthy controls (Atmaca et al., 2007). We also found that refractoriness to OCD might be associated with OFC and thalamus regions (Atmaca et al., 2006). Moreover, Chamberlain et al. (2008) reported reduction of activation of various cortical regions, including the lateral orbitofrontal cortex in OCD patients and their clinically unaffected relatives, suggesting the existence of an underlying previously undiscovered endophenotype for the disorder. Ahmari et al. (2013) used optogenetics in mice to simulate cortico-striato-thalamo-cortical circuit hyperactivation observed in OCD patients and determined that while acute OFC and ventromedial striatum stimulation did not provoke repetitive behaviors, repeated hyperactivation over multiple days generated a progressive increase in grooming, a mouse behavior related to OCD. In addition, Cecconi et al. (2008) detected that gray matter volumes were regionally increased in the right inferior frontal gyri in all 5 patients with refractory OCD one year after gamma ventral capsulotomy. As hippocampus-amygdala complex has important connections with OFC, it was thought to link between this complex and OCD itself (Lawrence et al., 1998; Phillips et al., 2003). Gray (1982) and Pitman (1987) imply that the hippocampus may play an important role in compulsive behavior. Van Laere et al. (2006) reported PET images obtained before and after high-frequency anterior capsular stimulation in 6 refractory OCD patients, demonstrating positive correlations between clinical improvement and the metabolic activity changes in left ventral striatum, left amygdala, and left hippocampus. Our study group speculated that hippocampus and amygdala abnormalities might be implicated in refractoriness to OCD (Atmaca et al., 2008).

4. Treatment

The mainstay of treatment for OCD consists of cognitive-behavioral therapy and psychotropic drug management, most frequently with SRIs. As mentioned in the Introduction section, an important part of OCD patients respond to serotonin reuptake inhibitors alone or in combination with other medications, and cognitive behavior therapy. However, up to 30%–40% of patients do not respond to the available treatment modalities (Saxena et al., 2001; Scarone et al., 1992; Robinson et al., 1995; Szeszko et al., 1999). The beginning treatment option is associated with the severity of OCD. Indeed, if patient has mild to moderate OCD in regard to severity, exposure and response prevention (ERP) or SRI alone can be administered (Seibell et al., 2013). But it should be noted that most medication trials to gain US Food and Drug Administration (FDA) approval in OCD need to only a 25% to 35% reduction in Y-BOCS scores as a benchmark of efficacy (Seibell and Hollander, 2014).

An important number of studies evaluated the efficiency of SSRIs for the management of OCD. In that studies, it has been showed that these drugs have generally a similar in efficacy (Soomro et al., 2008). Because