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Obsessive–compulsive disorder comorbidity: clinical assessment and therapeutic implications

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Obsessive–compulsive disorder (OCD) is a neuropsychiatric disorder affecting approximately 1–3% of the population. OCD is probably an etiologically heterogeneous condition. Individuals with OCD frequently have additional psychiatric disorders concomitantly or at some time during their lifetime. Recently, some authors proposed an OCD sub-classification based on comorbidity. An important issue in assessing comorbidity is the fact that the non-response to treatment often involves the presence of comorbid conditions. Non-responsive patients are more likely to meet criteria for comorbid axis I or axis II disorders and the presence of a specific comorbid condition could be a distinguishing feature in OCD, with influence on the treatment adequacy and outcome.

Keywords: OCD comorbidity, Schizo-OCD, OCD and psychosis, OCD and ADHD, OCD and anxiety disorders, OCD and mood disorders, OCD and neurological diseases

INTRODUCTION

Obsessive–compulsive disorder (OCD) is a neuropsychiatric disorder affecting approximately 1–3% of the population and it is characterized by recurrent intrusive ideas, impulses, or urges (obsessions) along with overt or covert behaviors (compulsions) aimed at reducing the distress (Karno et al., 1988; DSM-IV).

Obsessive–compulsive disorder was initially considered as a sub-dimension of depression, the so-called "ananchastic depression." In the 1980s this concept was questioned, demonstrating that only antidepressants with serotonin-reuptake inhibition activity were effective in treating obsessions and compulsions. In the last years, there has been another important paradigm shift, including other neurotransmittorial systems in the putative pathophysiological mechanisms underlying OCD, such as dopamine, glutamate, noradrenaline, and GABA. This leads to the crucial hypothesis that OCD may be an etiologically heterogeneous condition, therefore being affected by a wide spectrum of comorbidities. Individuals with OCD frequently have additional psychiatric disorders concomitantly or at some time during their lifetime (Angst et al., 2005). Recently, some authors proposed an OCD sub-classification based on comorbidity (Nestadt et al., 2009). The authors proposed a three classes solution characterized by: (1) an OCD simplex class, in which major depressive disorder (MDD) is the most frequent additional disorder; (2) an OCD comorbid tic-related class, in which tics are prominent and affective syndromes are considerably rarer; and (3) an OCD comorbid affective-related class in which panic disorder (PD) and affective syndromes are highly presented (Nestadt et al., 2009). Membership within a class is differentially associated with other clinical characteristics. For example, the OCD comorbid tic-related class is predominantly male and characterized by high consciousness. The OCD co-morbid affective-related class is predominantly female, has a young age at onset, obsessive–compulsive personality disorder features, high score on the "taboo" factor of OCD symptoms, and low consciousness.

An important issue in assessing comorbidity is the fact that non-response to treatment often involves the presence of comorbid conditions. Non-responsive patients are more likely to meet criteria for comorbid axis I or axis II disorders and the presence of a specific comorbid condition could be a distinguishing feature in OCD, with influence on the treatment adequacy and outcome (Pallanti and Quercioli, 2006). Particularly, comorbid conditions such as bipolar disorder (BD) and attention deficit hyperactivity disorder (ADHD) are common in treatment-resistant patients, but there are only few studies investigating their impact on treatment resistance (Magalhães et al., 2010; Sheppard et al., 2010).

The aim of this paper is to discuss clinical characteristics of OCD comorbidities and their implication in the management of OCD patients. We will review only the most clinical relevant comorbidities.

METHOD

In this paper we present a systematic review of papers focusing on OCD comorbidities. Data were extracted from published articles from the Medline database until May 2011. The keywords used for the research were various combinations of the following words: OCD, OCD comorbidities, BD, MDD, psychosis, ADHD, PD, social phobia, post-traumatic stress disorder (PTSD), epilepsy, stroke.

OCD AND MOOD DISORDERS

Epidemiology

Recent epidemiological and clinical studies confirmed the presence of a strong association between OCD and affective disorders (Kruger et al., 1995; McElroy et al., 2001).

The association between OCD and depression has been acknowledged since the nineteenth century (McIntyre et al., 2006).

Depression is the most frequent complication of OCD, as reported in several studies (El-Mallakh and Hollifield, 2008).

Denys et al. (2004) found that MDD was 10 times more prevalent in OCD patients than in general population. While up to 60–80% of patients with OCD experience a depressive episode in their lifetime, most studies agree that at least one-third of patients with OCD have concurrent MDD at the time of evaluation (Perugi et al., 1997; Tükel et al., 2002).

Comorbidity rates in reported studies vary widely from 19 to 90%; this is largely due to methodological and semantic differences (Overbeek et al., 2002).

Obsessive–compulsive morbidity is also one of the most disabling co-occurring conditions in bipolar disease (BD), and these symptoms are frequently encountered in clinical practice (El-Mallakh and Hollifield, 2008).

Bipolar comorbidity in obsessive–compulsive disorder (OCD) is a relevant phenomenon and has clinically significant influence on the symptomatological expression and complications of the disorder (D'Ambrosio et al., 2010).

Moreover, comorbidity with BD has relevant implications for treatment outcome, since bipolarity has a negative influence on compliance and response to currently available anti-obsessive agents (Krüger et al., 2000; Perugi et al., 2002; Hantouche et al., 2003).

A recent study individuated OCD as the most frequent anxiety disorder in bipolar patients throughout their lifetime (Zutshi et al., 2006).

In adults, evidence of a higher-than-expected overlap between OCD and BPD first came from the Epidemiological Catchment Area study, where 23% of those with BPD also met criteria for OCD (Robins and Price, 1991). Subsequent studies have consistently found a greater than expected overlap between OCD and BPD at rates as high as 15–35% (Joshi et al., 2010).

Clinical and epidemiological studies in recent years have suggested that the rate of lifetime comorbid BD in clinical and epidemiological samples of patients with obsessive–compulsive disorder (OCD) is up to 21.5% (Perugi et al., 1997; Hantouche et al., 2003; Faravelli et al., 2004).

In addition, many authors have concluded that the frequency of OCD is higher in bipolar patients than in general population (9–35% versus 1.5–2.3%; Cassano et al., 1999; McElroy et al., 2001; Simon et al., 2004). On the other hand, certain studies do not support these high rates of comorbidity (Vieta et al., 2001; Henry et al., 2003).

Family members of bipolar I and II affected individuals have higher rates of OCD (Coryell et al., 1985), which suggests a familial or genetic association. However, some researchers believe that obsessive–compulsive symptoms (OCS), particularly when episodic, may actually represent a variation of how bipolar illness is expressed and not a true comorbidity (Strakowski et al., 1998; Swartz and Shen, 1999).

When using a wider concept of bipolar spectrum in both clinical and epidemiological studies, lifetime comorbidity rates increased significantly: almost 50% of OCD cases manifest cyclothymic traits and/or some lifetime hypomanic symptoms (Hantouche et al., 2003).

Clinical characteristics and clinical course

The comorbidity of OCD and affective disorders strongly affects clinical features, treatment outcome, and prognosis of such patients.

As for the comorbidity with MDD, it is reported that most often OCD predates depression, suggesting that depressive symptoms usually occur in response to the distress and functional impairment associated with OCD (Ricciardi and McNally, 1995; Bartz and Hollander, 2006).

In addition, depressive symptoms seem to be more strongly associated with obsessive than with compulsive symptoms (Ricciardi and McNally, 1995).

The presence of comorbid MDD in OCD seems to relate to older age, severity and chronicity of OCS, number of hospitalizations, greater comorbidity with generalized anxiety disorder (GAD), simple phobias and caffeine abuse, higher frequency of aggressive obsessions, higher number of suicide attempts, and disability (Perugi et al., 2002; Tükel et al., 2006; Maina et al., 2007).

The clinician should also accurately investigate obsessive symptoms and differentiate it from ruminations, which are typically and exclusively focused on depressive thematics, but may sometimes appear similar in their clinical presentation.

The comorbidity of BD in OCD has relevant implications on the symptomatological expression and pharmacological treatment of the disorder.

Obsessive–compulsive disorder and BPD comorbidity in adults may herald an episodic course of OCD with higher rates of certain obsessions (aggressive/impulsive, sexual, religious, and obsessional doubts) and compulsions (compulsions of control, hoarding, ordering/arranging), which require more frequent hospitalizations and complex pharmacological interventions (Hantouche et al., 2003; Millet et al., 2004; Maina et al., 2007).

Bipolar subjects with OCD were more likely than those without OCD to have higher lifetime rates of thoughts of death and suicide and of suicide attempts (Freeman et al., 2002).

Furthermore, subjects with OCD and comorbid BD have higher rates of panic/agoraphobia, substance use disorders, and higher rates of narcissistic and antisocial personality disorders (Hantouche et al., 2003; Millet et al., 2004; Maina et al., 2007).

Similarly, the presence of OCD comorbidity has been reported to predict a more chronic course of BPD and greater frequency of major depressive episodes, with a trend toward poor response to mood stabilizers (Perugi et al., 2002; Zutshi et al., 2006)

Zutshi et al. described bipolar patients with a comorbid anxiety disorder as younger, mostly male, having earlier ages of disease onset, and higher rates of academic failure. These patients also have poor treatment response, higher rates of psychotic features, mixed episodes, suicide attempts, and substance abuse, more frequent hospitalizations, and a higher percentage of time spent in illness episodes (Cassano et al., 1999; Simon et al., 2004; Zutshi et al., 2006).

Some investigators have observed that OCD symptoms may vary during the course of BD. For example, cases have been reported in which OCD symptoms remitted during mania and reappeared with the remission of it and/or onset of depression (Keck et al., 1986; Gordon and Rasmussen, 1988). In addition,

authors have noted that patients with mixed mania may be more likely than patients with pure mania to have comorbid OCD (McElroy et al., 2001).

Treatment

The therapeutic implications of a comorbid depressive disorder in OCD are still poorly understood. Comorbidity affects the outcome of behavioral versus pharmacotherapeutic interventions. For example, in OCD, severe depression may worsen the prognosis for behavioral treatments, whereas most studies suggest that pharmacological treatment with selective serotonin reuptake inhibitors (SSRIs) is equally effective for OCD with or without concomitant depression (Overbeek et al., 2002).

Meta-analytic studies have shown that the beneficial effects of antidepressants such as clomipramine and SSRIs on OCD symptoms are unrelated to the presence of depressive symptoms. Hollander et al. (1991) state that depressive symptoms interfere with the response to both psychopharmacologic and behavioral treatments of OCD. Also, Foa (1979) reported that the outcome of behavioral therapy is negatively influenced by the presence of severe depressive symptoms.

However, although comorbid depressive disorder might alter treatment outcome, it has little impact on the psychopharmacological strategy, as serotonin reuptake inhibitors (SRI) are first line treatment for both conditions.

Instead, the comorbidity of OCD with BD is a difficult therapeutic challenge because the pharmacological treatments of the two illnesses diverge and medications used to manage OCD can exacerbate BD symptoms.

The centerpiece of pharmacologic treatment of OCD is the use of the serotoninergic antidepressants and these agents have repeatedly demonstrated both acute and prophylactic efficacy and are currently considered first line agents (Pallanti et al., 2002; Hollifield et al., 2006).

Unfortunately, the use of antidepressants may be problematic in bipolar illness. Specifically, antidepressants may induce manic episodes, destabilize the illness over time by increasing the number of both manic and depressive episodes, or induce a chronic depressive state (El-Mallakh and Karippot, 2005, 2006).

A small amount of controlled data is available concerning the treatment of BD complicated by OCD. However, adequate mood stabilization should be achieved before antidepressants are used to treat OCD symptoms in order to minimize antidepressant-induced mania or cycling (Freeman et al., 2002).

In the past years, reports have pointed out a potential role for atypical antipsychotics (AAP) in the treatment of OCD that is resistant to SRI. In particular, there is positive evidence for risperidone, haloperidol, olanzapine, and quetiapine (Goodwin et al., 2009).

Reviews and meta-analyses of randomized controlled trials suggest the efficacy of aripiprazole in the acute treatment and maintenance treatment of manic episodes. Moreover, adjunctive aripiprazole seems to be effective in improving response rate in patients with MDD. Some studies suggest a role for aripiprazole in the treatment of OCD. These reports include aripiprazole augmentation of SRI in treatment-resistant OCD, or in patients with schizophrenia comorbid OCS (Glick et al., 2008; Arbaizar et al., 2009; McIntyre, 2010).

Mood stabilizers may also have an effect in OCD but have not been extensively studied (El-Mallakh and Hollifield, 2008). While these agents are second line choices for the treatment of OCD patients without bipolar illness, they become usually first line agents in bipolar subjects. However, they are generally suboptimal in the control of anxiety symptoms and carry a higher side effects burden than serotoninergic antidepressants (El-Mallakh and Hollifield, 2008). Non-pharmacologic approaches, such as cognitive behavioral psychotherapy (CBT) and transcranial magnetic stimulation may have an important role, which should be formally tested in this situation (Magalhães et al., 2010). Raja et al. suggest that, from a therapeutic point of view, it should be given hierarchical priority of a bipolar diagnosis even when the criteria for a DSM-IV-TR OCD diagnosis are fully met and when bipolar symptoms are sub-threshold. Whatever the intensity of OCD symptoms, current, or past presence of signs or symptoms consistent with BD, or a familial load for BD, should suggest caution in prescribing SSRI treatment (Raja and Azzoni, 2004).

They propose as a safer first line choice a treatment with mood stabilizers (lithium plus anticonvulsants, or electroconvulsive therapy). In some patients, especially those who manifest psychotic symptoms, a combination of mood stabilizers, and second-generation antipsychotics is required. Even if AAP have sometimes been reported to exacerbate OCD symptoms, these drugs are effective in the treatment of OCD symptoms in bipolar spectrum–OCD patients (Raja and Azzoni, 2004).

Mood stabilization should be achieved as a first objective. In unresponsive patients, addition of low doses of SSRI could be considered, while strictly monitoring emerging symptoms of (hypo)mania or mixed states. In some cases, the best option may be to look for a reasonable compromise between potential anti-OCD effectiveness and detrimental effect on OCD (Raja and Azzoni, 2004).

OCD AND PSYCHOSIS

Epidemiology

The relationship between OCD and psychosis has been a matter of dispute for many years. The first description of OCD in psychiatric literature by Jeremy Taylor in the mid-seventeenth century was a patient with intrusive thoughts that developed into paranoid delusion (Hunter and MacAlpine, 1963). Co-occurrence of OCS and psychotic disorders was first recognized over a century ago (Berrios, 1989). Recently, interest in this area has increased considerably, probably due to the recognition of higher-than-expected comorbidity rates and the observation of emergence, or exacerbation, of OCS during treatment with AAP. (Ghaemi et al., 1995; Khullar et al., 2001; de Haan et al., 2002; Lykouras et al., 2003; Alevizos et al., 2004).

There is growing evidence that patients with comorbid OCD and schizophrenia (recently termed "schizo-obsessive"; Hwang and Hollander, 1993; Zohar, 1997) appear to have distinct patterns of psychopathology, course of illness, psychiatric comorbidity, neurocognitive deficits, and treatment response, compared to their schizophrenic counterparts, suggesting the existence of a separate

subgroup on the schizophrenia spectrum (Poyurovsky et al., 2004; Lysaker and Whitney, 2009).

The prevalence of comorbid OCD and schizophrenia was estimated at 12.2% by the US National Institute for Mental Health Epidemiologic Catchment Area Study (Karno et al., 1988). Recent studies reported that approximately 8–26% of schizophrenic patients met the DSM-IV criteria for OCD (Eisen et al., 1997; Porto et al., 1997; Poyurovsky et al., 1999, 2001; Bermanzohn et al., 2000; Tibbo et al., 2000; de Haan et al., 2002; Nechmad et al., 2003; Ohta et al., 2003; Byerly et al., 2005). However, other investigators have reported rates up to 59.2% (Bland et al., 1987). A common bias in these estimates of comorbidity lies in the enrollment of patients with OCS and not strictly OCD. Obviously, when patients with OCS are included, the true comorbidity of OCD and psychosis may be grossly overestimated. However, the two conditions appear to co-occur more commonly than their lifetime prevalence rates of 1–1.5% and 2–3%, respectively, suggest. Finally, several studies investigating OCD comorbidity reported that 10–60% of schizophrenic patients have OCS (Fenton and McGlashan, 1986; Bland et al., 1987; Berman et al., 1995a, 1998; Lysaker et al., 2000; Okasha et al., 2000; Fabisch et al., 2001; Kayahan et al., 2005).

Clinical characteristics and clinical course

In a clinical perspective, differentiating an obsession from a delusion represents a difficult but important challenge because of its impact on the choice of treatment. Difficulty is due to the fact that assessment of insight alone can not resolve the distinction between an obsession and a delusion. Indeed, the *Diagnostic and Statistical of Mental Disorders*, fourth edition (DSM-IV), allows for the diagnosis of OCD with the specifier "with poor insight." So in front of an obsession with poor insight the differential diagnosis of delusion should be based on other criteria. Bottas et al. (2005) in their review of the schizo-obsessive subtype of schizophrenia gave six suggestions to identify OCS in the schizophrenic patient. The first suggestion is that the types of obsessions and compulsions observed in schizophrenia are phenomenologically similar to those present in pure OCD. According to this observation, a recent study identified five Y-BOCS symptom dimensions in schizophrenic patients that did not correlate with schizophrenia symptom dimensions and that were comparable to those revealed in "pure" OCD (Faragian et al., 2009).

With regards to behavioral assessment it is important to underline that a repetitious act or behavior should be considered a compulsion only if it occurs in response to an obsession and not if it occurs in response to psychotic ideation (e.g., repetitive checking in response to paranoid fears does not constitute a compulsion). In the same way, the clinician should differentiate between compulsions and simple motor stereotypies, which are repetitive or ritualistic movement or postures, automatic, patterned, and periodic, but that not take place in order to relieve anxiety and obsessive thoughts.

In the assessment of thought disorders the authors suggest to not consider a recurrent, intrusive, ego-dystonic thought as an obsession if it revolves exclusively around current delusional themes (e.g., violent images, which constitute a common type of obsession in OCD, may represent an entirely different phenomenological entity in the context of psychosis).

Similarly, there are other conditions in which we must exercise caution in the evaluation of OCS. Indeed, OCS may be difficult to distinguish in the presence of thought form disorder. Nevertheless, primary obsessional slowness may be mistaken for prodromal schizophrenia or thought disorder; such patients may be unable to articulate any obsessions and may exhibit no compulsions. Finally, at times it may not be possible to determine if apparent OCS in the presence of psychosis represent real OCS; in such cases empiric treatment with a neuroleptic and a serotonin reuptake inhibitor (the standard treatment for OCD) may be necessary (Bottas et al., 2005).

Classically, early investigators argued that OCS might precede the onset of schizophrenia because they could retard or prevent the "personality disintegration" associated with psychosis (Stengel, 1945).

Several studies investigated the onset of OCD in schizophrenic patients; in these studies the onset of OCD preceded or co-occurred with the onset of schizophrenia in 47–76% and succeeded schizophrenia onset in only 23–25% of patients (Poyurovsky et al., 2003, 2008). Furthermore, OCS and OCD seem to be frequent also in the UHR (ultra high risk syndrome); indeed, a recent investigation found a prevalence of OCD of 14–20% in a sample of UHR youth (Niedman et al., 2009).

Compared with schizophrenic patients, schizo-obsessive patients show a different pattern of comorbidity, with a preferential aggregation of OCD–spectrum disorders, namely body dysmorphic disorder, eating disorders, and tic disorders, but not major depressive, substance abuse, or anxiety disorders (Poyurosky et al., 2006).

A fairly large number of studies have assessed, as a primary or a secondary aim, the impact of OCS or OCD on the severity of psychotic symptoms, and on the general outcome in schizophrenic patients. Taken individually, these studies have yielded heterogeneous results. Recently, a meta-analysis of these studies, including 1096 patients, showed that the impact of OCS and OCD on the severity of psychotic symptoms was dependent on the definition of OCS. When a categorical definition was used, no differences were found between OCD–schizophrenia and non-OCD schizophrenia, whereas when a dimensional definition was used, OCS–schizophrenia showed a greater severity of psychotic symptoms than non-OCS schizophrenia (Cunill et al., 2009). These findings suggest the possibility that comorbidity with OCD in schizophrenia differs from schizophrenia exhibiting OCS without the diagnosis of OCD. Accordingly, a recent Japanese study, found that schizophrenic patients with OCS exhibited significantly earlier onset of schizophrenia, lower socioeconomic status, and more severe psychiatric symptoms than those without OCS. Earlier hospitalizations, familiar history of psychosis, more severe schizophrenic symptoms, were associated with OCS comorbidity. Moreover, negative symptoms were associated with OCD comorbidity in chronic schizophrenia (Owashi et al., 2010).

The data regarding the influence of OCD comorbidity on suicide risk are controversial. Recently, two studies reported that these patients have more suicidal ideation and a higher rate of suicide attempts compared to those without OCD (Ucok et al., 2006; Sevincok et al., 2007). However other studies failed to find this association (Ucok et al., 2011).

Cognitive and neuropsychological impairment in schizo-obsessive and schizophrenic patients has been investigated in several studies, but results are often inconsistent. Pallanti et al. (2009) conducted the first neurophysiological examination comparing schizo-OCD with OCD, schizophrenic patients, and healthy controls. Schizo-OCD showed a distinct event-related potential pattern (intermediate between that of OCD and schizophrenic patients) suggesting the presence of a less functional impairment in schizo-OCD compared to schizophrenic patients and arguing that schizo-OCD may not only be a distinct clinical entity from pure OCD and schizophrenia, but it may also be characterized by a distinguishable neurophysiologic pattern (Pallanti et al., 2009).

Treatment

Evidence regarding therapeutic options for treating OCD and OCS in schizo-obsessive patients is limited and treatment itself represents a major challenge because of the emerging evidence of AAP-induced OCS. Since the introduction of AAP, both case reports (Diler et al., 2003; Lykouras et al., 2003; Alevizos et al., 2004; Ke et al., 2004; Ozer et al., 2006; Stamouli and Lykouras, 2006) and clinical studies (Baker et al., 1992; de Haan et al., 1999; Ertugrul et al., 2005) have described *de novo* onset of OCS during treatment with these drugs. Conventional neuroleptics with high D_2-blocking potency, such as haloperidol and pimozide, do not seem to worsen OCD while the lower potency conventional neuroleptic chlorpromazine induced OCS in two patients (Howland, 1996). Most reports of APP-induced OCS in schizophrenic patients are related to clozapine, risperidone, olanzapine, and quetiapine (Ghaemi et al., 1995; Baker et al., 1996; Khullar et al., 2001; Reznik et al., 2004; Tranulis et al., 2005). A possible explanation of this phenomenon could be the involvement of $5HT_{2A}$ receptors and the disruption of the interaction of serotonin and dopamine within the cortico-striato-thalamocortical loops (Kapur and Remington, 1996). However, data from a recent genetic association study also suggested a glutamate involvement in APP-induced OCS (Kwon et al., 2009).

A randomized double-blind study comparing olanzapine with risperidone in patients with early psychosis found a difference in Y-BOCS scores decreases, with olanzapine showing more efficacy. However, these results have several limitations because Y-BOCS scores only decreased significantly in mild OCS (Y-BOCS > 10) subgroup.

Therefore, the choice of antipsychotic treatment in schizo-obsessive patients is still difficult and only a few trials specifically investigated the treatment of OCS or OCD in schizo-obsessive patients. However, interesting data are emerging from the use of aripiprazole (the atypical antipsychotic with the higher D_2 – receptor affinity) and lamotrigine (an anticonvulsant inhibiting glutamate release). Glick et al. (2008) conducted an open-label 6 week trial of aripiprazole monotherapy in 15 schizophrenic patients presenting OCS. Each patient switched from the ongoing antipsychotic medication to aripiprazole monotherapy. At the end of the trial six of the seven patients completing the study showed an improvement on the Y-BOCS score of greater than 35% from baseline to week 6.

Poyurovsky et al. (2010) conducted an 8 weeks open-label trial of lamotrigine augmentation in schizo-obsessive patients. Five of nine study participant were responders to add-on lamotrigine ($\geq$35% reduction in Y-BOCS score); the OCS-attenuating effect of lamotrigine was not accompanied by improvement of schizophrenia symptoms supporting the notion that OCS are independent of core schizophrenia symptoms in schizo-obsessive patients. Current evidence supports the use of AAP in combination with an SRI for the schizo-obsessive patients, but these findings are based on a small sample sizes. The SRIs specifically recommended are clomipramine, fluvoxamine, and sertraline (Berman et al., 1995b; Poyurovsky and Weizman, 1998; Rahman et al., 1998; Reznik and Sirota, 2000; Dwivedi et al., 2002).

OCD AND OTHER ANXIETY DISORDERS

Epidemiology

In DSM-IV OCD has been classified as an anxiety disorder together with PD, PTSD, and GAD. This nosological solution has not been entirely satisfactory because of the peculiarity of OC phenomena (Storch et al., 2008; Stein et al., 2010). However, the growing evidence that OCD has much in common with other anxiety disorders despite its specific features (Storch et al., 2008; Radua et al., 2010; Stein et al., 2010) has led to the realization that it would be inappropriate to remove it from the group of anxiety disorders in DSM-5. This has dampened down the enthusiasm for obsessive–compulsive spectrum disorders (OCSDs) as a separate diagnostic group. As a result, the current proposal is to classify OCSDs along with anxiety disorders to form a larger group tentatively called "anxiety and OCSDs" (Taylor and Vaidya, 2009; Phillips et al., 2010).

Lifetime comorbidity between OCD and other anxiety disorders has been identified as 22% for specific phobia, 18% for social anxiety disorder (social phobia), 12% for PD (Pigott et al., 1994), and 30% for GAD. Therefore, it is clear that an accurate assessment of OCD and anxiety comorbidities is necessary to achieve a proper treatment and a good response to it.

Clinical characteristics, clinical course, and treatment

Panic disorder. The comorbidity between OCD and PD is extremely high (13–56%). There are many similarities between symptoms of OCD and PD, for example the hypochondriac polarization and the excess of risk assessment that can be present in both disorders. For some authors this fact can explain the effectiveness of the same treatments for both disorders. Several evidences suggested that CBT is effective in both OCD and PD. Thus, CBT plus SSRI, can be an appropriate treatment when PD and OCD are in comorbidity. Finally, increasing evidences indicate that the γ-aminobutyric acid (GABA) system is important in the pathophysiology of PD (Guttmacher et al., 1983). This could be a new field for the treatment of comorbid PD in OCD.

Generalized anxiety. Generalized anxiety disorder is a current and typically chronic mental disorder with prevalence in the general population of around 6% (Murphy and Leighton, 2008). It is characterized by inappropriate or excessive anxiety and worrying that persists over time and is not restricted to a particular set of circumstances. The specific comorbidity of OCD and GAD in adults is high, particularly among individuals with OCD. Both Andrews et al. (1990) and reported over 30% of adults with OCD have a lifetime history of GAD.

The difficulty in distinguishing between the two disorders is given by a considerable overlap between the worries in GAD and the obsessions in OCD. Recent conceptualizations of GAD and OCD have also emphasized the similarities between the functions of worries in GAD and compulsions in OCD (Comer et al., 2004), such as distortion of probabilistic thinking, risk overvaluation, apprehensiveness. However, the two disorders are generally distinguished by the fact that worries in GAD represent more excessive concerns about realistic situations, while obsessions in OCD are considered to be alien to the individual (i.e., ego-dystonic) and more bizarre in nature (Barlow, 2002). Abramowitz and Foa found that OCD with comorbid GAD was associated with higher rates of indecisiveness and pathological responsibility among adults (Abramowitz and Foa, 1998).

Selective serotonin reuptake inhibitors are effective in both disorders; however, if there is an unsatisfactory clinical response several studies support the use of other drug augmentations.

Aliyev and Aliyev (2008) demonstrated the efficacy of Valproate for the management of GAD in a double-blind, placebo-controlled randomized trial involving 80 male patients. Thus, valproate plus SSRIs can be a good augmentation strategy in OCD/GAD patients. Furthermore, AAP are known to be effective in the treatment of resistant OCD. The addition of an atypical antipsychotic [low-dose risperidone (Brawman-Mintzer et al., 2006) or olanzapine augmentation of fluoxetine (Pollack et al., 2006)] in GAD patients who do not respond adequately to first line treatments may provide additional benefit. Thus, the atypical antipsychotic augmentation of an SSRI in an OCD/GAD patient may represent a more effective treatment.

Finally, several trials suggested that Gabapentin and Pregabalin (Rickels et al., 1990; Feltner et al., 2003) are both effective in treating GAD. Our opinion is that they can be a good association therapy with an SSRI in treating an OCD patient with GAD comorbidity.

Post-traumatic stress disorder. Post-traumatic stress disorder and OCD share several common elements in symptomatology. Both are characterized by repeated intrusive thoughts; both include avoidant behavior that severely interferes with daily functioning and is directed by the need to avoid any cue, object, or place that causes distress. Both involve compulsions that are performed in order to reduce anxiety (de Silva and Marks, 1999, 2001). From an etiological perspective, both PTSD and OCD are associated with classical conditioning to an anxiety-provoking stimulus; this connection between stimulus and anxiety, in turn, is reinforced by behaviors that reduce anxiety (de Silva and Marks, 1999; Zohar et al., 2009). Many studies have attempted to explore the link between trauma and OCD symptoms. Recently, Zohar et al. described a case series of five Israeli veterans who were diagnosed with both PTSD and OCD following combat trauma (Zohar J. 2011, Personal Communication). In this case series the content of the obsessions was quite different from the intrusive symptoms of PTSD. The thoughts, flashbacks, or psychological distress in response to reminders of the trauma in PTSD were different from the general obsessive thoughts at the OCD side of the diagnosis, which included fear of contamination, disgust of dirt, and doubt. Moreover, in this case series, the generalized OCD cues were typical of OCD (e.g., garbage, excessive washing, public toilets, etc). Similarly, the compulsions were typical of OCD (e.g., washing and checking, and unrelated to the trauma). Thus, the authors argued that the course of the symptoms suggests a potential environmental role in the development of OCD following an exposure to traumatic event, suggesting a biological linkage between exposure to trauma and OCD.

In conclusion, there is a clear need for specific and accurate assessment of an OCD patient with another anxiety disorder in order to start a more specific and effective treatment.

OCD AND NEUROLOGICAL DISEASES

Anxiety disorders frequently occur in individuals with neurologic illnesses. Anxiety may be a symptom of a reaction to a neurologic disorder, a medication side effect, or a comorbid condition. The most common anxiety disorders seen in neurologic patients are PD, GAD, social phobia, and OCD. Very often, these conditions are unrecognized (and therefore untreated) or are attributed to being a normal response to having a neurologic illness. However, if they are not treated, anxiety disorders can significantly increase morbidity and mortality in neurologic patients (Davies et al., 2001).

Obsessive–compulsive disorder has for long been associated with epilepsy. Particularly, 10–22% of patients with temporal lobe epilepsy (TLE) may have OCD. These patients show a high rate of obsessions of washing, symmetry/exactness, and ordering, with greater preoccupation concerning certain aspects of religion, compared with controls or patients with idiopathic generalized epilepsy. Furthermore, discrete anatomic lesions in these pathways, or their surgical removal, may induce (or conversely) improve OCD in TLE patients (Kaplan, 2010).

Obsessive–compulsive disorder is frequently described in patients with primarily basal ganglia dysfunction, such as Tourette's syndrome, Sydenham's chorea, Huntington's disease, and von Economo's encephalitis (Miguel et al., 1997). Several studies found a high prevalence of OCS and OCD also in Parkinson's disease, but some others did not (Maia et al., 2003; Harbishettara et al., 2005). Furthermore, Pallanti et al. (2010) described the onset of a complex repetitive behavior (defined as "pounding") after bilateral subthalamic nucleus stimulation in Parkinson's patients. Pounding has been interpreted as a compulsive behavior and is defined as a stereotypic motor behavior characterized by an intense fascination with repetitive purposeless movements, such as taking a part mechanical objects, handling common objects as if they were new and entertaining and continuously picking at oneself, etc.

An acute onset of OCD may occur after stroke injury. This kind of OCD onset has been associated with inferior parietal (Simpson and Baldwin, 1995), basal ganglia (Carmin et al., 2002), orbitofrontal (Kim and Lee, 2002), caudate (Thobois et al., 2004), and posterior frontal (Swoboda and Jenike, 1995) infarcts and traumatic orbitofrontal lesions (Ogai et al., 2005), further implicating these structures in the pathogenesis of OCD. However, a recent study reported a case of a patient suffering with severe OCD whose symptoms disappeared immediately following a small right posterior fronto-parietal infarct.

Post-streptococcal autoimmunity is hypothesized to be an additional etiologic pathway in a subset of children with OCD and tic disorders (Swedo et al., 1998). This subset of children experiences a sudden onset of OCD and/or motor tics in association with Group A streptococcal (GAS) infections (e.g., "strep throat"), a disorder classified as pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). Although the clinical presentation of PANDAS was described over 10 years ago by Swedo et al. (1998), it still remains controversial because a direct evidence of a distinct pathogenic mechanism has yet to be found in human studies.

Roughly one-third to one-half of children with Tourette syndrome (TS) or chronic tic disorder will experience comorbid OCD throughout their lifetime (Bloch et al., 2006a). OCD symptoms in patients with TS have an onset around the time that the tics reach their worst-ever, but symptoms may also appear *de novo* in adulthood. OCD patients with comorbid tics tend to have greater rates of symmetry obsessions, and counting, repeating, ordering, and arranging compulsions than OCD patients without comorbid tic symptoms (Leckman et al., 1994). In terms of pharmacotherapy, children with OCD and comorbid tics are likely to have a worse response to SSRIs than children without comorbid tics (March et al., 2007). While children with OCD and comorbid tics may not respond optimally to SSRIs, it has been shown that children with OCD, with and without comorbid tics, appear to have a similar response to cognitive behavioral therapy (March et al., 2007). Another treatment option for OCD patients with comorbid tics is antipsychotic medication. A meta-analysis of antipsychotic augmentation trials for treatment refractory OCD suggests that OCD patients with comorbid tics may have an improved response to this intervention (Hollander et al., 1991; Bloch et al., 2006b).

Obsessive–compulsive disorder – attention deficit hyperactivity disorder

Compulsivity and impulsivity are defined the former as the feeling of being forced to perform certain action in order to relieve stress or anxiety and the latter as the proneness to act without adequate forethought. At first glance they may be considered as two opposite behavioral features, but actually seem to be closely related in certain clinical entities. Pathological gambling or substance abuse disorders can be considered as an example: classically considered as highly impulsive diseases, they both share compulsive features. From this perspective, the frequent comorbidity between OCD and ADHD is not surprising, and probably suggests an overlap in their neurobiological underpinnings.

Attention deficit hyperactivity disorder is a common childhood-onset neurodevelopmental disorder that occurs in approximately 5% of the population, which frequently co-occurs with OCD (Faraone et al., 2003). This relationship is of interest for several reasons:

(1) Due to the fact that both of the two conditions may present symptoms of inattention, differentiating between primary attentive symptoms and attentive symptoms secondary to anxiety disorders is of crucial relevance for prognosis, and treatment (de Geus et al., 2007).

(2) The evidence that ADHD and OCD are frequently comorbid with TS (de Geus et al., 2007), suggests that these three disorders may be etiologically related (Comings and Comings, 1985; Kadesjo and Gillberg, 2000; Gaze et al., 2006).

(3) Family studies suggest that OCD and ADHD may co-segregate in families, and this could be useful in correctly diagnosing a disorder (Geller et al., 2007a,b).

The ADHD prevalence rate among OCD patients varies widely, ranging from 0 to 51% (Geller et al., 2001; Jaisoorya et al., 2003). This could be an effect of differences in data acquisition, sample size, age of participants, recruitment sources, and inclusion/exclusion criteria in the considered studies.

As already noted, both OCD and ADHD are highly comorbid with TS, a tic disorder with a prevalence of 0.5–1% (Gaze et al., 2006; Stewart et al., 2009).

Patients with the attentive subtype of ADHD (also called ADD) frequently develop compulsive coping styles. They very often do not have a complete overview of tasks and try to manage confusion and disorganization using extra control. The clinician should try to differentiate a perfectionist coping style from an OCD. A way of doing it could be to ask the patient what will happen if control cannot be performed. If irritation arises, it is more likely to be ADHD; if there is anxiety or panic, OCD should be considered first (Kooij, 2010).

In a recent study Sheppard et al. (2010) found a higher rate of ADHD in a sample of individuals with childhood-onset OCD than in the general ADHD population sample; the strongest association was found between ADHD and clinically significant hoarding behavior. Hoarding is defined as the excessive acquisition and failure to discard worthless items as they accumulate, leading to distress or impairment, including the inability to use work or living spaces (Frost and Gross, 1993; Steketee and Frost, 2005; Iervolino et al., 2009; Mueller et al., 2009). Prevalence rates range from 18 to 40%, and hoarding seems to occur in many psychiatric conditions, in particular OCD (Frost et al., 1996). In Sheppard's study in total, 41.9% of participants with ADHD also had hoarding behaviors compared to the 29.2% of participants without ADHD.

CONCLUSION

Current research on animal and human models suggests that the discovery of more precise and distinctive neurofunctional targets is possible and that may successfully lead to a patient-tailored treatment algorithm. Identifying the different groups of patients and basing the treatment on reliable and easily detectable neurodysfunctional targets is one of the most desirable and exciting goals that in the next future may be achieved, in order to offer a highly specific treatment for each single patient.

In the next years neuroscientific researches will provide a better definition of the dysfunction implicated in the pathophysiology of OCD. This process will improve the definition of different neurodysfunctional treatment targets. Thus, the treatment of OCD and of its comorbidities will become more neurodysfunctional guided.

Another important goal will probably be the possibility to differentiate between the simple co-occurrence of two or

more syndromes and a real comorbidity, that represent two distinct clinical situations, in order to explain why different OCD sub-groups show different comorbidities patterns. This may be due to the relationship between the neurobiological underpinnings of OCD and of its comorbid conditions, which could have a consistent overlap. As an example, it can be hypothesized that the sub-group of OCD patients with affective disorders comorbidity could have pathophysiological mechanisms that are different from that of OCD/tic disorders sub-group, therefore allowing us to exclude the concept of simple co-occurrence.

However, this is an operation that in our opinion should be substantiated by strong and accurate biological evidences, and further research is needed in the field.

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