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Immune system and obsessive-compulsive disorder

Donatella Marazziti[a,*], Federico Mucci[a], Leonardo F. Fontenelle[b]

[a] Dipartimento di Medicina Clinica e Sperimentale, Section of Psychiatry, University of Pisa, and Brain Research Foundation Lucca, Italy
[b] Universidade Federal do Rio de Janeiro, IDOR, MONASH University, Brazil

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ABSTRACT

Background: Recently, much attention has been devoted to the possible alterations of the immune system in obsessive-compulsive disorder (OCD). Therefore, the aim of this paper was to review the current literature on the relationships between OCD and immune system.
Methods: A PubMed and Google Scholar search was performed with specific keywords.
Results: In the childhood, much emphasis has been given to the relationship between group A Streptococcus (GAS) infection and the development of a group of clinical syndromes characterized by neuropsychiatric symptoms known as "pediatric autoimmune neuropsychiatric disorders associated with streptococcus" (PANDAS). However, more recently, PANDAS has been reconsidered and evolved towards pediatric acute-onset neuropsychiatric syndrome (PANS) and/or Childhood Acute Neuropsychiatric Syndrome (CANS) all characterized by the presence of typical of OCD symptoms and tics. In adult OCD patients, different immunological parameters have been described to differ from those of healthy control subjects, although a few numbers of studies were carred out and most of them performed in small samples.
Conclusions: Although the exact relationships between OCD and immune processes are still unclear, available literature supports their role in the pathophysiology of OCD, while providing a fascinating hint for possible immunotherapeutic treatments in OCD.

1. Introduction

During the last decades, the interest devoted to the relationship between the nervous and immune systems has been gradually increasing, up to the point of becoming one of the most fascinating current research topics in medicine. Indeed, a growing bulk of literature has supported the existence of complex and dynamic interactions between the two systems, and how their interplay might be involved in both healthy and pathological conditions (Kerr et al., 2005; Marazziti et al., 2015). Not surprisingly, dysfunctions of the immune system and/or related alterations the hypothalamic-pituitary axis (HPA) have been implicated in the pathophysiology of several neurological and psychiatric disorders (Kerr et al., 2005), such as Alzheimer's disease (AD), Parkinson's disease (PD), HIV encephalopathy, multiple sclerosis (MS), transverse myelitis (TM), depression, dementia, schizophrenia, post-traumatic stress disorder, panic disorder, social phobia, and even obsessive-compulsive disorder (OCD) (Brambilla et al., 1999; Dell'Osso et al., 2016; Hinze-Selch and Pollmacher, 2001; Kaplin et al., 2005; Leonard and Myint, 2006; Maes et al., 1999; Marazziti et al., 2015; Rapaport and Stein, 1994; Wilson et al., 2002).

Obsessive-compulsive disorder (OCD) is the fourth most common psychiatric disorder, with a prevalence of about 2.5% in the general population, and a similar gender distribution, except in the adolescence when the male to female prevalence ratio is 3:1. In the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders, (DSM-5), together with related disorders, OCD has been considered an autonomous condition no longer subsumed under anxiety disorders (APA, 2014). Obsessions and compulsions represent its patognomonic symptoms. The term "obsession" refers to an idea, a thought, a word, a memory, a feeling, an impulse or a mental image that intrudes into the consciousness against the will of the subject, who usually recognizes its irrational nature. It typically causes marked anxiety or distress, leading the patient to attempt to neutralize the obsession with some other thoughts or actions. A "compulsion" is defined as a drive, an impulse, or a behavior that the patient feels forced to perform, often in response to an obsession (APA, 2014). These behaviors are generally not realistically linked with what they are supposed to prevent or neutralize, or are clearly excessive. To be diagnosed as OCD, obsessions and/or compulsive behaviors must provoke significant subjective distress, consume a substantial part of the day (e.g. at least one hour per day) or interfere with the social and working adjustment (APA, 2014).

The typical OCD patient usually struggles against compulsive

* Corresponding author at: Dipartimento di Medicina Clinica e Sperimentale, Section of Psychiatry, University of Pisa, Via Roma 67, 56100 Pisa, Italy.
E-mail address: dmarazzi@psico.med.unipi.it (D. Marazziti).

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behaviors and intrusive thoughts in different ways and to different degrees. In the DSM-5, there has been great importance to the dimensional, rather than categorical nature of insight into OCD symptoms, which can now be described as good or fair, poor, or absent (i.e., complete conviction that OCD beliefs are true). Subjects in their childhood, with schizotypal personality, or with primitive thought process (the so-called "magic thinking"), may show no or poor insight and may attribute a particular meaning and/or significance to the compulsive behaviors (APA, 2014).

The first-line treatment of OCD is based on selective serotonin (5-HT) reuptake inhibitors (SSRIs) and the tricyclic (TCA) clomipramine, given the crucial role of serotonin (5-HT) system in its pathophysiology, or cognitive-behaviour therapy (CBT) (Janardhan Reddy et al., 2017). However, treatment resistance is still a major problem in OCD for involving 30%-40% of OCD patients, as it is the delayed therapeutic effect of available compounds, which usually take between two and six months to occur (Marazziti and Dell'Osso, 2015). The therapeutic failures in OCD are a clear indicator that the pathophysiology of OCD, focused mainly on 5-HT, also involves other neurotransmitters (such as dopamine or glutamate) and may be insufficient for the management of the whole disorder (Marazziti et al., 2017). For these reasons, the immune system have been proposed as a putative pharmacological target for novel antiobsessional drugs, although the mechanisms would be different in childhood and adulthood (Murphy and Pichichero, 2002; Murphy et al., 2006; Teixeira et al., 2014). The aim of this paper was to review current literature through a PubMed and Google Scholar search of published data highlighting the possible involvement of the immune systems in childhood and adult OCD and suggesting novel pathogenetic mechanisms.

2. Methods

The systematic review was carried out according to the PRISMA guidelines (Moher et al., 2009) through searching PubMed and Google Scholar for English language papers from January 1990 to January 31, 2018. The keywords used and combined with "OCD" or "OCD symptoms" were "Childood" or "Adulthood" or "Pathophysiology"; or "Immune System"; "Cytokines"or "Streptococcus Infections"; or PANDAS" or "PANS"or "CANS" or"Antiobsessional Drugs".

Articles were searched by all authors: they agreed not to include conference abstracts or posters, while case reports were considered if published in indexed journal. The following inclusion criteria were adopted: studies carried out in clinical sample of children/adolescents and/or adult; reliable diagnosis of OCD according to structured interviews and standardized criteria; and use of reliable laboratory tests for biological measures

3. Results

A total of 205 papers were included in the review, of which 115 were on PANDAS + PANS + CANS, 46 on immune system in OCD (23 in adults and 23 in children/adolescents) and 44 on cytokines in OCD (31 in adults and 13 in children/adolescents).

3.1. Immune system in childhood OCD

In children, infections by group A beta-hemolytic streptococcus (GAS) have been associated with immune system responses and the development of rheumatic fever (RF), neurological symptoms [such as Sydenham chorea (SC)], and psychiatric syndromes, such as OCD and tics. Although the incidence of pediatric GAS infections is extremely high, it is remarkable than only a minority of children with such infection may show such neuropsychiatric symptoms: this strongly suggests that there is a certain individual vulnerability to develop OCD and tics with GAS (Murphy et al., 2006).

The risk of developing OCD seems to occur only during acute episodes of RF (Murphy et al., 2006). Family studies suggest that this relationship could be familial, as OCD-related and anxiety disorders, such as generalized anxiety disorders and separation anxiety, aggregate more frequently in first-degree relatives of RF probands, when compared with control subjects (Dale, 2005; Ravindran et al., 1999). An interesting finding in the search for candidate genes is the association of two polymorphisms of the promoter region of the tumor necrsosi factor (TNF)-α gene with both OCD and RF, as TNF-α is a proinflammatory cytokine involved in RF and several other autoimmune diseases (Fluitman et al., 2010; Hounie et al., 2007). According to some authors, this finding might indicate a shared genetic vulnerability (Seixas et al., 2008). The relationship between RF and OCD is strongly supported by the clinical evidence of high incidence of obsessions and/or compulsions not only in SC subjects (Ramasawmy et al., 2007; Texeira et al., 2014), but also in children with GAS infection without SC (Swedo, 1994; Asbahr et al., 1998; Mercadante et al., 2000; Murphy et al., 2006;). Two decades ago, the National Institutes of Mental Health group devoted to OCD study proposed the term "pediatric autoimmune neuropsychiatric disorders associated with streptococcus (PANDAS)" for those syndromes characterized by both OCD symptoms, specifically obsessions and compulsions, and choreiform movements (Murphy and Pichichero, 2002; Murphy et al., 2006; Swedo et al., 1997; Swedo et al., 1998). In PANDAS, cross-reacting antibodies against putamen have been observed, the so-called D8-17 (Mercadante et al., 2000; Perlmutter et al., 1999), although their exact role and that of autoimmune processes in these conditions are still unclear (Murphy et al., 2006; Perlmutter et al., 1999), as it is the specificity of D8-17 (Brilot et al., 2011). However, the validity of this condition has been recently questioned (Mataix-Cols et al., 2017), as the available data cast doubts about the role of GAS: Therefore new categories have been described, the so-called PANS (Pediatric Acute-onset Neuropsychiatric Syndrome) and CANS (Childhood Acute Neuropsychiatric Syndrome). These conditions would encompass psychiatric symptoms with abrupt OCD with or without tics, without being associated with any infection, inflamation or any other trigger (Baytunca et al., 2016; Chang et al., 2015; Gerardi et al., 2015; Murphy et al., 2015a; Orefici et al., 2016; Toufexis et al., 2015). This is supported by the results of a recent nationwide survey carried out in Sweden indicating a familial link between autoimmune disorders, not limited to streptococcus-related conditions and both OCD and Tourette/chronic tics disorders. The authors postulate that some additional mother-specific factors, such as the placental transmission of antibodies, could be involved (Mataix-Cols et al., 2017).

3.2. Immune system in adulthood OCD

There exists a series of studies suggesting that immune system might play a role in the pathophysiology of adult OCD. It should be immediately underlined that the avialable data are with no doubt interesting, albeit sparse. Indeed, some clinical evidences show that immune-related diseases (such as systemic lupus erythematosus, thyroid dysfunctions, and others) are more common in OCD than in other psychiatric disorders (da Rocha et al., 2008; Hoekstra and Minderaa, 2005; Murphy et al., 2006, Dinn et al., 2001; Miguel et al., 1995; Placidi et al., 1998; Tinelli et al., 2013). In any case more recent data, gathered through large populations studies put into question this association that is defined "uncertain" (Mataix-Cols et al., 2017; Perez-Vigil et al., 2016).

The possible role of autoimmune processes in adult OCD is suggested by the decreased levels of peripheral T–cells that have been related to symptom severity (Konuk et al., 2007; Sayyah et al., 2011), but also by the presence of anti-basal ganglia antibodies (Nicholson et al., 2012). Decreased natural killer (NK) cell activity increased CD8+ and decreased CD4+ lymphocytes have been also described in adult OCD patients and interpreted as stress indices (Marazziti et al., 1999). Moreover, reduced IL-1β levels (Brambilla et al., 1997), and a trend toward low LPS-stimulated IL-6 levels still in adult OCD patients have