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Review article

The link between autoimmune diseases and obsessive-compulsive and tic disorders: A systematic review

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ABSTRACT

Immunological factors are increasingly recognized as being important in a range of neuropsychiatric disorders. We aimed to summarize the disperse and often conflicting literature on the potential association between autoimmune diseases (ADs) and obsessive-compulsive disorder (OCD) and tic disorders. We searched PubMed, EMBASE, and PsycINFO for original studies evaluating the relationship between ADs and OCD/tic disorders until July, 13th 2016. Seventy-four studies met inclusion criteria. Overall, the studies were of limited methodological quality. Rates of OCD were higher in rheumatic fever patients who were also affected by its neurological manifestation, Sydenham's chorea. The literature on other ADs was scarce and the findings inconclusive. Few studies examined the association between ADs and tic disorders. A handful of family studies reported elevated rates of ADs in first-degree relatives of individuals with OCD/tic disorders, and vice versa, potentially suggesting shared genetic and/or environmental mechanisms. In conclusion, at present, there is modest evidence for a possible association and familial co-aggregation between ADs and OCD/tic disorders. We offer some suggestions for future research.

Contents

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1. Introduction

Obsessive-compulsive disorder (OCD) is a relatively common psychiatric disorder with a lifetime prevalence of 2.3% (Ruscio et al., 2010), similar in both genders (American Psychiatric Association, 2013). OCD is defined by recurrent intrusive thoughts or images (obsessions) that create significant distress and drive individuals to perform repetitive behaviors or mental rituals (compulsions) in an attempt to reduce the distress (American Psychiatric Association, 2013). Tic disorders, including Tourette's Disorder (TD), are childhood-onset, neurodevelopmental movement disorders characterized by persistent motor and/or vocal tics lasting for more than one year (American Psychiatric Association, 2013). The prevalence of chronic tic disorders is estimated to be around 0.3% to 1% of the population and is much more common in boys than in girls (Knight et al., 2012; Scharf et al., 2012).

The etiologies of OCD and tic disorders are currently unknown, but the conditions are thought to be closely related. OCD and tic disorders share phenomenology and co-aggregate in families (Pauls, 2010; Pauls et al., 1995), and this familiality is largely due to substantial shared genetic liability (Davis et al., 2013; Pinto et al., 2016). Moreover, both disorders have alterations in overlapping cortico-striato-thalamic systems (Amat et al., 2006; Lewis and Kim, 2009), further supporting the idea of a shared biological vulnerability.

In addition to genetic factors, autoimmunity might also play a role in the etiology of these disorders (Davison, 2012; Murphy and Husted, 2004; Najjar et al., 2013). However, the involvement of immunological factors demonstrated in classical autoimmune diseases (ADs) in the pathogenesis of OCD/tic disorders has been inconclusive (Teixeira et al., 2014).

Based on the mechanism of rheumatic fever (RF), a well-defined AD, and its major neurological manifestation, Sydenham's chorea (SC), Swedo and colleagues proposed a link between OCD and OCD-related disorders and autoimmunity (Swedo et al., 1998). Following a group-A beta-hemolytic streptococcal (GAS) infection, a subgroup of children was found to develop the so-called Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS), which included obsessive-compulsive symptoms (OCS) or tics, without meeting the criteria for SC (Swedo et al., 1998). The validity of PANDAS as an independent entity has been widely debated and has evolved to a further conceptualization – the Pediatric Acute- onset Neuropsychiatric Syndrome (PANS) – that no longer requires the evidence of infection (Swedo et al., 2012). Although the exact mechanism remains to be elucidated, molecular mimicry in which antibodies initially develop to respond to a GAS infection and cross-react with neural epitopes has been suggested as a possible developing path (Cunningham, 2014; Garvey et al., 1998; Swedo et al., 1998).

In line with this theoretical link, patients with RF or other ADs, such as systemic lupus erythematosus (SLE), multiple sclerosis (MS), or antiphospholipid syndrome, have also been suggested to present higher rates of OCD and, to a lesser extent, tic disorders (de Alvarenga et al., 2009; Foroughipour et al., 2012; Slattery et al., 2004; Toren et al., 1994). However, the literature linking ADs and OCD or tic disorders is large, methodologically diverse and difficult to reconcile. It is possible that ADs and OCD/tic disorders share a common genetic vulnerability (Hounie et al., 2008). Although gene-searching efforts in OCD and tic disorders are in their infancy (Mattheisen et al., 2015; Scharf et al., 2013), genes involved in the pathogenesis of several ADs – such as polymorphisms of the tumor necrosis factor-α (TNF-α) – (Gu et al., 2010; Ishizuka et al., 1999; Jimenez-Morales et al., 2009; Nada and Labib, 2011; Popa et al., 2011; Ramasawmy et al., 2007; Song et al., 2014) have been associated with OCD/tic disorders in some studies (Cappi et al., 2012; Keszler et al., 2014; Rao et al., 2015) but not others (Denys et al., 2004).

In this context, we conducted the first systematic review investigating whether there is an association between ADs and OCD or tic disorders, either in individuals with ADs and OCD or tic disorders themselves, or in their relatives. Because common ADs tend to coexist in the same individuals and co-aggregate in the same families (Cardenas-Roldan et al., 2013; Cooper et al., 2009; Sardu et al., 2012; Somers et al., 2006), finding an above-chance association between ADs and OCD/tics, would support a possible role of the immune system in the etiology of these disorders. We also aimed to examine whether this association is stronger in specific ADs. Knowing that specific ADs are more frequently associated with these psychiatric symptoms may lead to a better understanding of the role that the immune system plays in these disorders, and also help guiding gene- searching and gene by environment interaction studies. Finally, we suggest some specific research strategies to help the field move forward.

2. Methods

The review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist and protocol outlined by the PRISMA Group (Moher et al., 2009).

2.1. Eligibility criteria

Studies meeting the following criteria were included: 1) presented information on the association between ADs and OCD/OCS or tic disorders; 2) were original research (i.e., not reviews, editorials, or commentaries); 3) used standardized diagnostic criteria or validated rating scales for symptom severity; 4) presented outcomes using risk measures with confidence intervals (CI), proportions, or means and standard deviations (sd); and 5) were controlled studies or, if a control group was not available, included well-characterized clinical cohorts. Exclusion criteria were: 1) studies solely based on PANDAS cases since the construct is under

debate and the definition itself implies an autoimmune process; or 2) case reports or case series.

2.2. Information sources

PubMed, EMBASE, and PsycINFO were searched up until November, 20th 2015 for published and unpublished studies evaluating the association between ADs and OCD/OCS or tic disorders. Additional papers were identified from reference lists of included studies and relevant reviews. The search was updated in July, 13th 2016.

2.3. Search

The search strategy combined terms referring to: a) OCD/OCS or tic disorders, b) general terms for ADs (e.g., *autoimmune disorder*, *autoimmune pathology*, *immune disorder*), and c) 36 specific ADs retrieved from a list from the American Autoimmune Related Disorders Association (available in the Supplementary material). These 36 ADs were selected for either having central nervous system manifestations or being prevalent and well characterized among the ADs group. We also used medical subject headings (MeSH) terms and corresponding key words in titles and abstracts. Results from the keywords were combined and duplicates removed subsequently. No age, setting, geographic, language, date, or publication status restrictions were applied. Full details of the search strategy can be found in the Supplementary material.

2.4. Study selection

Each study was initially screened for eligibility at the title and abstract level independently by two authors. For relevant studies, the full text was also screened independently by two authors. Disagreements between the authors were resolved via discussion until a consensus was reached.

2.5. Data collection process

Data extraction was performed independently by two authors. Where data were not available in the original research, the corresponding author was contacted and data were requested.

For each article identified, we extracted information on study characteristics (authors, publication year, sample size), study design (e.g., case-control study, prospective cohort study, cross-sectional study), participant characteristics (e.g., AD, psychiatric diagnosis/symptoms of interest, sex and age of the participants), OCD/OCS or tic disorder assessment method (e.g., structured interview, rating scale), AD assessment method (e.g., standard criteria, laboratory tests), and OCD/OCS or tic disorder outcome.

3. Results

3.1. Study selection

A total of 2584 studies were retrieved from the search. Among these, 734 duplicates were identified and removed. The remaining 1856 studies were analyzed for inclusion. Six additional publications were identified through other sources. The full texts of 104 studies considered relevant were assessed for eligibility. Of these, 74 met inclusion criteria and were included in the systematic review. The PRISMA flowchart is shown in Fig. 1.

3.2. Study characteristics

Of the 74 eligible studies, 62 reported on the association between ADs and OCD/OCS, five on the association between ADs and tic disorders, and seven reported on the association between ADs and both OCD and tic disorders. All studies but two (Asbahr et al., 2005a; Dalsgaard et al., 2015) employed a cross-sectional design. All studies were based on small to moderate sample sizes (n = 11–678), except for two epidemiological studies that included 5117 (Chu et al., 2012) and 2242 cases (Dalsgaard et al., 2015). Fifteen of the 74 studies included pediatric samples. Thirty-nine studies had a control group. Fifty studies reported categorical outcomes (in 13 studies, psychiatric diagnoses were established via clinical interviews, in 34 studies diagnoses were established via semi- structured interviews, in one study the diagnosis was register-based, and in two studies the method of diagnosis was not reported). Twenty-six studies reported continuous outcomes describing severity of symptoms using symptom severity scales. Two studies reported both categorical (OCD diagnosis) and continuous (symptom severity) outcomes (Abbas et al., 1996; Maia et al., 2005). Sixty-nine studies reported rates of OCD/OCS or tic disorders in individuals with ADs, and the five remaining studies reported rates of ADs in samples of individuals with OCD/tic disorders. Regarding the types of ADs, most studies reported on the association between OCD/OCS or tic disorders and RF (19 studies), followed by MS (12 studies), SLE (6 studies), inflammatory bowel disease (IBD; 5 studies), and insulin-dependent diabetes mellitus (IDDM; 5 studies). The rest reported on other systemic ADs (13 studies), other organ-specific ADs (11 studies), or both systematic and other organ-specific ADs (2 studies). Five of the 74 eligible articles were family-based studies.

3.3. Rheumatic fever

Sixteen studies reported on the association between RF and OCD/OCS (Table 1). Of these, eight studies focused on RF when accompanied by SC (Abbas et al., 1996; Asbahr et al., 2005a, 1998; Faustino et al., 2003; Hounie et al., 2004; Maia et al., 2005; Moreira et al., 2014; Swedo et al., 1989). Two case-control studies (Abbas et al., 1996; Maia et al., 2005) showed that OCD was significantly more frequent among RF cases that also met criteria for SC than among healthy subjects. The study by Maia et al. (2005) also reported higher rates of OCD in RF cases with SC than in RF cases without SC, and no differences between non-SC RF cases and healthy controls. A third case-control study found the same trend among RF cases with SC compared to healthy controls and the non-SC RF group, without reaching statistical significance (Hounie et al., 2004). Out of four studies without any control group looking at RF cases plus SC, three reported a prevalence of OCD much higher than the expected for the general population (16.7–38.4%) (Asbahr et al., 2005a, 1998; Moreira et al., 2014), while the fourth study did not find any OCD cases in their sample of 19 patients (Faustino et al., 2003). Of note, the study by Asbahr et al. (2005a) only included RF patients who had already developed OCS. The studies by Abbas et al. (1996) and Maia et al. (2005) also assessed OCS among RF patients using the Leyton Obsessional Inventory (LOI) (Abbas et al., 1996), the LOI child version (LOI-CV), and the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (Maia et al., 2005). Both studies found significantly higher scores in RF cases that also had SC, compared to healthy controls. Maia et al. (2005) also found significantly higher OCS in RF cases without SC, compared to healthy controls. Two further studies also used the LOI-CV to assess OCS in RF with and without SC, without any comparison group (Asbahr et al., 1998; Swedo et al., 1989). Asbahr et al. (1998) reported that children with RF and SC scored significantly higher on resistance and interference subscales compared to RF cases without SC during only the first two months after the onset of the RF. Swedo et al. (1989) reported that children who had been affected by RF and SC scored higher on symptoms and interference subscales than children with RF without SC.

Table 1
Studies examining the link between Rheumatic Fever and OCD/OCS or tic disorders.

Study *author (year)*	Sample size *n*	Age *mean (sd)*	Gender *% females*	Study design	AD assessment	OCD/OCS or tic disorders assessment	Assessors blind to AD status	OCD/OCS or tic disorders outcomes
Obsessive-Compulsive Disorder in Rheumatic Fever + Sydenham's Chorea								
Abbas et al. (1996)	20 cases/78 controls (medical students)	Cases: 18.24 (5.21) Controls: 19.74 (4.21)	Cases: 65.00% Controls: 24.36%	Case-control, cross-sectional	Revised Jones criteria	Clinical interview by a psychiatrist	Not reported	OCD diagnosed in 4 (20%) RF cases and 0 controls ($\chi^2 = 16.264$; $p = 0.000$).
Asbahr et al. (1998)	50 cases (30 with SC and 20 without SC)	Children, age not reported	RF + SC: 56.7% RF-SC: 50.0%	Cross-sectional	Jones criteria	K-SADS	N/A	OCD diagnosed in 5 RF + SC cases (16.7% of the RF + SC sample, 10% of the whole RF sample, with or without SC).
Asbahr et al. (2005a)	73 cases who had developed OCS	Children, age not reported	54.8%	Cross-sectional	Not reported	K-SADS, DICA	N/A	OCD diagnosed in 28 (38.4%) RF + SC cases.
Faustino et al. (2003)	19 cases	11.7 range: 7–15	79%	Cross-sectional	Jones criteria	Clinical interview by a psychiatrist	N/A	OCD diagnosed in 0 RF + SC cases.
Hounie et al. (2004)	59 cases (28 with SC and 31 without SC)/39 controls from an orthopedic clinic	RF + SC: 14.14 (3.15) RF-SC: 14.55 (5.66) Controls: 11.51 (3.28)	Cases: 56.9% Controls: 38.5%	Case-control, cross-sectional	Jones criteria	K-SADS, SCID	Yes	OCD diagnosed in 3.85% (95% CI = 3.7-3.9) of RF + SC cases (n = 1), 0% of RF-SC cases, and 2.56% (95% CI = 2.51-2.60) of controls (n = 1). OCD + subclinical OCD in 8.65% (95% CI = 8.54-8.76) of RF + SC cases (n = 2), 0% in RF-SC cases, and in 2.56% (95% CI 2.51-2.60) of controls (n = 1).
Maia et al. (2005)	106 cases (56 with SC and 50 without SC)/50 controls (healthy individuals)	RF + SC: 13.3 (2.9) RF-SC 13.3 (2.8) Controls: 12.4 (3.1)	RF + SC: 58.9% RF-SC: 50% Controls: 70%	Case-control, cross-sectional	Jones criteria	K-SADS	Not reported	OCD diagnosed in 13 (23.2%) RF + SC cases, 3 (6%) RF-SC cases, and 2 (4%) healthy subjects ($p = 0.003$).
Moreira et al. (2014)	50 cases	21.5 (6.7)	80%	Cross-sectional	Jones criteria	MINI	N/A	OCD diagnosed in 12 (24%) RF + SC cases.
Obsessive-Compulsive Symptoms in Rheumatic Fever + Sydenham's Chorea								
Abbas et al. (1996)	20 cases/78 controls (medical students)	Cases: 18.24 (5.21) Controls: 19.74 (4.21)	Cases: 65% Controls: 24.36%	Case-control, cross-sectional	Jones criteria	LOI	Not reported	Cases scored significantly higher than controls in all LOI scales (symptoms: 12.35 ± 9.08 and 7.43 ± 2.31, respectively, $p < 0.01$; trait: 5.90 ± 4.37 and 3.85 ± 2.74, respectively, $p < 0.005$; interference: 11.66 ± 14.62 and 4.12 ± 3.82, respectively, $p < 0.001$; resistance: 9.05 ± 11.88 and 3.73 ± 2.74, respectively, $p < 0.01$).
Asbahr et al. (1998)	50 cases (30 with SC and 20 without SC)	Children, age not reported	RF + SC: 56.7% RF-SC: 50.0%	Prospective	Jones criteria	LOI-CV	N/A	Cases scored higher than controls in the resistance (4.30 ± 5.21 and 0.90 ± 1.37, respectively; Mann-Whitney = 435.5, $p = 0.005$) and interference (3.63 ± 3.83 and 0.80 ± 1.24, respectively; Mann-Whitney = 427.5, $p = 0.008$) scales of the LOI at the first assessment during the first two months. Differences were not significant at 3–4 months and 5–6 months follow-up.

Table 1 (*Continued*)

Study *author (year)*	Sample size *n*	Age *mean (sd)*	Gender *% females*	Study design	AD assessment	OCD/OCS or tic disorders assessment	Assessors blind to AD status	OCD/OCS or tic disorders outcomes
Maia et al. (2005)	106 cases (56 with SC and 50 without SC)/50 controls (healthy individuals)	RF + SC: 13.3 (2.9) RF-SC: 13.3 (2.8) Controls: 12.4 (3.1)	RF + SC: 58.9% RF-SC: 50%50% Controls: 70%	Case-control, cross-sectional	Jones criteria	LOI-CV, Y-BOCS	Not reported	Higher LOI-CV and Y-BOCS scores in RF + SC cases vs controls (p = 0.002 and 0.014, respectively) and in RF-SC cases vs controls (p = 0.030 and 0.015, respectively).
Swedo et al. (1989)	37 cases (23 with SC and 14 without SC)	Children, age not reported	48.65%	Cross-sectional	Not reported	LOI-CV	N/A	Higher LOI-CV scores in SC cases vs controls in 'yes' (8.00 ± 4.1 and 4.29 ± 3.6; t = 5.58; p = 0.004) and interference items (9.64 ± 9.4 and 2.93 ± 3.7; t = 6.02; p = 0.003).
Obsessive-Compulsive Disorders in Rheumatic Fever (without specifying whether Sydenham's Chorea is present)								
Alvarenga et al. (2006b)	51 cases/46 controls (patients with heart-related conditions with no RF history)	Cases: 31.47 (8.40) Controls: 33.37 (9.14)	Not reported, but no significant differences regarding frequency of gender between groups	Case-control, cross-sectional	Modified Jones criteria	Clinical interview by a psychiatrist based on DSM-IV criteria + best estimate diagnosis procedure	Yes	OCD diagnosed in 3 (5.9%) RF cases and 1 (2.2%) control (p = 0.349).
da Silva et al. (2011)	135 cases/58 controls (whole sample had mechanical valve prostheses)	Women: 53.0 (11.1) Men: 52.9 (13.1)	59.1%	Case-control, cross-sectional	Patient survey complemented with medical record information	MINI	Yes	OCD diagnosed in 4.4% of RF cases and 1.7% of controls (p = 0.35).
Alvarenga et al. (2006a)	50 cases	34.5 (9.8)	72%	Cross-sectional	Jones criteria	SCID	N/A	OCD diagnosed in 1 (2%) case.
Ashfaq et al. (2007)	100 cases (rheumatic heart disease)	33.09 (9.22)	67%	Cross-sectional	Jones criteria	MINI	N/A	Lifetime OCD diagnosed in 10 (10%) cases. Lifetime subclinical OCD diagnosed in 3 (3%) cases. Current OCD diagnosed in 9 (9%) cases. Current subclinical OCD diagnosed in 3 (3%) cases.
de Alvarenga et al. (2009)	13 cases/665 controls (whole sample were patients with psychiatric disorders)	Whole sample: 33.63 (16.23) Cases: 37.00 (10.55) Controls: 33.50 (16.32)	44.7%, no significant differences between groups	Cross-sectional	Assessment of patients records + complementary clinical interviews by a private cardiologist or pediatrician	Clinical interview by a psychiatrist based on DSM-IV criteria + best estimate diagnosis procedure	Yes	OCD diagnosed in 8 (61.5%) RF cases and 233 (35.0%) controls (p = 0.302). Subclinical OCD in 12 cases (92.3%) and 352 (52.9%) controls (p = 0.025). OCSD (including OCD, subclinical OCD, tic disorders, TTM, and BDD) in 13 (100%) cases and 393 (59.1%) controls (p = 0.007).
Mercadante et al. (2000)	42 cases (22 with SC and 20 without SC)/20 controls with no ADs	RF + SC: 10.6 (2.8) RF-SC 10.7 (2.7) Controls: 10.7 (2.7)	Not reported	Case-control, cross-sectional	Jones criteria	K-SADS-E	Effort made but proved impossible due to SC's overt symptoms	OCD diagnosed in 5 (11.9%) cases (not specified whether they had SC) and in 0 controls (non-significant difference).
Sampaio et al. (2009)	58 cases	13.93	55.2%	Cross-sectional	Jones criteria	SCID-I/P, K-SADS	N/A	OCD diagnosed in 1 (1.7%) case. Subclinical OCD in 1 (1.7%) case. Any OCSD (including OCD, tic disorders, body dysmorphic disorder and pathologic 'grooming' habits –TTM, pathologic onychophagia and skin picking) diagnosed in 7 (12.1%) cases.

Table 1 (*Continued*)

Study *author (year)*	Sample size *n*	Age *mean (sd)*	Gender *% females*	Study design	AD assessment	OCD/OCS or tic disorders assessment	Assessors blind to AD status	OCD/OCS or tic disorders outcomes
Obsessive-Compulsive Symptoms in Rheumatic Fever (without specifying whether Sydenham's Chorea is present)								
Asbahr et al. (2005b)	38 cases/19 controls (IDDM patients)	RF: 20.55 (9.23) IDDM: 20.63 (16.69)	RF: 71% IDDM: 58%	Cross-sectional	Modified Jones criteria	Y-BOCS	N/A	Y-BOCS mean scores of 6.86 (sd = 6.79) in RF group and 4.89 (sd = 5.87) in IDDM group ($p = 0.935$).
Tic Disorders in Rheumatic Fever + Sydenham's Chorea								
de Alvarenga et al. (2009)	13 cases/665 controls (whole sample were patients with psychiatric disorders)	Whole sample: 33.63 (16.23) Cases: 37 (10.55) Controls: 33.5 (16.32)	44.7%, no significant differences between groups	Cross-sectional	Assessment of patients records plus clinical interviews by a cardiologist or pediatrician	Clinical interview by a psychiatrist based on DSM-IV criteria + best estimate diagnosis procedure	Yes	Tic disorders diagnosed in 4 (30.8%) cases and 81 (12.2%) controls ($p = 0.961$). OCSD (including OCD, subclinical OCD, tic disorders, TTM, and BDD) in 13 (100%) cases and 393 (59.1%) controls ($p = 0.007$).
Hounie et al. (2004)	59 cases (28 with SC and 31 without SC)/39 controls from an orthopedic clinic	RF + SC: 14.14 (3.15) RF-SC: 14.55 (5.66) Controls: 11.51 (3.28)	Cases: 56.9 Controls: 38.5	Case-control, cross-sectional	Jones criteria	K-SADS, SCID	Yes	1. TD diagnosed in 7.17% of RF cases and 0 controls (7.41% RF + SC and 7.26% RF-SC). 2. CTD diagnosed in 6.26% of RF cases and 0 controls (3.85% RF + SC and 7.14% RF-SC). 3. Transient tic disorders diagnosed in 11.22% of RF cases and 0 controls (19.62% RF + SC and 3.33% RF-SC). 4. TD + CTD diagnosed in 13.43% of RF cases and 0 controls (11.11% RF + SC and 14.39% RF-SC). Comparisons 2, 3, 4, and all comparisons between the total RF group vs controls are significantly different ($p < 0.05$).
Mercadante et al. (2000)	42 cases (22 with SC and 20 without SC)/20 controls with no ADs	RF + SC: 10.6 (2.8) RF-SC: 10.7 (2.7) Controls: 10.7 (2.7)	Not reported	Case-control, cross-sectional	Jones criteria	K-SADS-E	Effort made but proved impossible due to SC's overt symptoms	Tic disorders diagnosed in 20 (47.6%) cases (16 cases RF + SC and 4 RF-SC) and 2 (10%) controls (significantly higher in cases; $p < 0.01$; RF + SC group was significantly different from RF-SC; $p < 0.01$).
Sampaio et al. (2009)	58 cases	13.93	55.2%	Cross-sectional	Jones criteria	SCID-I/P, K-SADS	Not reported	TD or chronic tic disorders diagnosed in 5 (8.6%) cases.
Walker et al. (2005)	42 cases	9.8 (range 3–13)	50%	Cross-sectional	Clinical and laboratory assessment	Clinical interview by a psychiatrist, according to DSM-IV criteria	Not reported	TD diagnosed in 5 (11.90%) cases.

Abbreviations: AD autoimmune disease; BDD body dysmorphic disorder; CIDI Composite International Diagnostic Interview; DIS diagnostic interview schedule; DICA Diagnostic Interview for Children and Adolescents; DSM-III Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition; DSM-III-R Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition revised; DSM-IV Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; ICD-9 The International Classification of Diseases, Ninth Revision; IDDM insulin dependent diabetes mellitus; K-SADS Schedule for Affective Disorders and Schizophrenia for School-Age Children; KSADS-E Schedule for Affective Disorders and Schizophrenia for School-Age Children—Epidemiologic Version; K-SADS-PL K-SADS Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime; LOI-CV Leyton Obsessional Inventory Child version; LOI Leyton Obsessional Inventory; OCD obsessive-compulsive disorder; OCS obsessive compulsive symptoms; OCSD obsessive compulsive spectrum disorders; OR Odds Ratio; MINI Mini International Neuropsychiatric Interview; MOCI Maudsley Obsessional-Compulsive Inventory; N/A not applicable; SC Sydenham's chorea; SCID-CV Structured clinical interview for DSM-IV Clinician Version; SCID Structured Clinical Interview for DSM-IV; SCID-I/P Structured clinical interview for DSM-IV Patient edition; SCID-UP-R Structural Clinical Interview for DSM III-R Upjohn-version; TD Tourette's disorder; TTM trichotillomania; Y-BOCS Yale-Brown Obsessive Compulsive Scale.

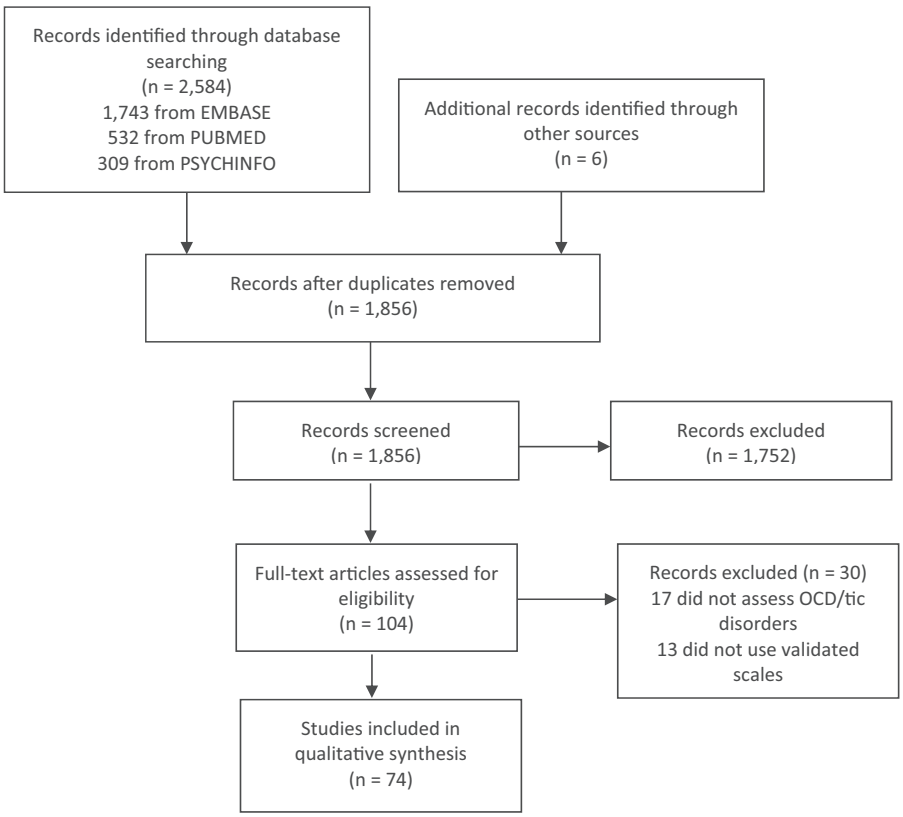

Fig. 1. PRISMA inclusion flow chart.

Eight studies examined the association between RF (without specifying whether SC was also present) and OCD/OCS (Alvarenga et al., 2006a,b; Asbahr et al., 2005b; Ashfaq et al., 2007; da Silva et al., 2011; de Alvarenga et al., 2009; Mercadante et al., 2000; Sampaio et al., 2009). Of those, four studies found a similar prevalence of OCD in RF cases and control groups with other heart-related conditions (Alvarenga et al., 2006b), mechanical valve prostheses (da Silva et al., 2011), non-RF psychiatric patients (de Alvarenga et al., 2009), or healthy individuals (Mercadante et al., 2000). Another four studies with no control group (Alvarenga et al., 2006a; Asbahr et al., 2005b; Ashfaq et al., 2007; Sampaio et al., 2009) showed mixed results. Two reported prevalence rates higher than expected (9 and 10%) (Asbahr et al., 1998; Ashfaq et al., 2007), while the other two showed prevalence rates within the expected population range (1.7-2%) (Alvarenga et al., 2006a; Sampaio et al., 2009). Asbahr et al. (2005b) used the Y-BOCS to compare severity of OCS in patients with RF and patients with IDDM. Scores were within the non-pathological range and there were no differences between the two ADs groups.

Five studies reported on the relation between RF and tic disorders (de Alvarenga et al., 2009; Hounie et al., 2004; Mercadante et al., 2000; Sampaio et al., 2009; Walker et al., 2005). Two studies (Hounie et al., 2004; Mercadante et al., 2000) found significantly higher rates of tic disorders among pediatric RF cases who also suffered from SC than in their respective controls without RF. The second study also found a significantly higher rate of tic disorders in RF cases unaffected by SC (Mercadante et al., 2000). One study (de Alvarenga et al., 2009) found a similar prevalence of tic disorders between psychiatric patients with and without RF. In two studies without control groups, one examined patients with RF and SC (Walker et al., 2005) and reported a frequency of TD of 11.9%, while the other (Sampaio et al., 2009), reporting on patients with RF (without specifying SC status), found a prevalence of 8.6%.

Taken together, there seems to be a positive association between SC and OCD/OCS and tic disorders. However, the association remains unclear when RF occurs in the absence of SC. These studies need to be interpreted in the context of a number of methodological limitations, including modest sample sizes, unblinded assessors, and the use of sub-optimal self-report measures, such as the LOI (King et al., 1995; Stewart et al., 2005; Storch et al., 2011; Wolff and Wolff, 1991).

3.4. Multiple sclerosis

Twelve studies reported on the association between MS and OCD/OCS (Table 2). Shabani et al. (2007) found a significantly higher prevalence of OCD in a group of patients with MS than in healthy controls, whereas Galeazzi et al. (2005) and Espinola-Nadurille et al. (2010) found no significant differences in the rate of OCD between MS cases and their respective matched controls. Four of five studies in MS patients without a control group (De Cerqueira et al., 2015; Foroughipour et al., 2012; Korostil and Feinstein, 2007; Uguz et al., 2008; Weisbrot et al., 2014), reported a higher prevalence of OCD than expected in the general population (4 to 16.1%) (Foroughipour et al., 2012; Korostil and Feinstein, 2007; Uguz et al., 2008; Weisbrot et al., 2014), and one did not (De Cerqueira et al., 2015).

All four studies that examined severity of OCS in MS patients used the SCL-90 (or its revised version, SCL-90-R), and they all reported significantly higher severity of OCS, compared to their respective matched healthy controls (Liu et al., 2009; Pires-Barata et al., 2009; Sarisoy et al., 2013; Shamsaei et al., 2015). However, the SLC-90 is considered a poor measure of OCS (Woody et al., 1995).

In sum, based on the limited available data, there may be a significant association between MS and OCD/OCS, but the methodological quality of the studies precludes firm conclusions. Of note, the only case-control study that employed blinded raters (Galeazzi

Table 2
Studies examining the link between Multiple Sclerosis and OCD/OCS.

Study author (year)	Sample size n	Age mean (sd)	Gender % females	Study design	AD assessment	OCD/OCS assessment	Assessors blind to AD status	OCD/OCS outcomes
De Cerqueira et al. (2015)	60 cases	43 (11.8)	76.7%	Cross-sectional	McDonald criteria	MINI	N/A	OCD diagnosed in 0 cases.
Espinola-Nadurille et al. (2010)	37 cases/37 controls (healthy individuals)	Cases: 36.3 (11.5) Controls: 39.88 (11.5)	Cases: 64.8% Controls: 59.4%	Case-control, cross-sectional	McDonald criteria	SCID	Not reported	OCD diagnosed in 1 (2.77%) case and 1 (2.77%) control (not significant differences).
Foroughipour et al. (2012)	112 cases	31.9 (range 14–48)	75%	Cross-sectional	McDonald criteria	Clinical interview by a psychiatrist	N/A	OCD diagnosed in 18 (16.1%) cases.
Galeazzi et al. (2005)	50 cases/50 controls (healthy individuals)	Cases: 34.9 (9) Controls: 33.7 (8.7)	Cases: 52% Controls: 54%	Case-control, cross-sectional	Poser criteria and Kurtzke Expanded Disability Status Scale (EDSS) score of $\leq$3.5	SCID	Yes	OCD diagnosed in 5 (10%) cases and 2 (4%) controls (OR = 2.67, 95% CI = 0.49–14.44).
Korostil and Feinstein (2007)	140 cases	43.9 (10.7)	74%	Cross-sectional	McDonald criteria	SCID	N/A	Lifetime OCD diagnosed in 12 (8.6%) cases.
Liu et al. (2009)	41 cases/41 controls (healthy individuals)	Cases: 37.44 (12.24) Controls: 36.38 (12.84)	Cases: 63.4% Controls: 63.4%	Case-control, cross-sectional	Poser criteria	SCL-90 obsessive-compulsive subscale	Not reported	Higher scores ($p = 0.009$) in cases (2.05 ± 0.69) compared to controls (1.55 ± 0.58).
Pires-Barata et al. (2009)	68 cases/30 controls (matched healthy individuals)	Cases: 37 (9.3) Controls: Not reported but matched	Cases: 74.3% Controls: Not reported but matched	Case-control, cross-sectional	McDonald criteria	SCL-90 obsessive-compulsive subscale	No	Higher scores in cases (1.8 ± 0.4) compared to controls (1.1 ± 0.5).
Sarisoy et al. (2013)	76 cases/76 controls (matched healthy individuals)	Cases: 37.84 (10.21) Controls: 36.67 (10.74)	Cases: 73.7% Controls: 68.4%	Case-control, cross-sectional	McDonald criteria	SCL-90-R obsessive-compulsive subscale	Not reported	Higher scores ($p = 0.000$) in cases (1.98 ± 1.02) compared to controls (1.13 ± 0.70).
Shabani et al. (2007)	85 cases/85 controls (healthy individuals)	Cases: 47.6 (10.2) Controls: 47.5 (10.4)	Cases: 52.9% Controls: 54.1%	Case-control, cross-sectional	McDonald, Poser, and Schumacher criteria	Clinical interview based on DSM-IV-TR criteria	Not reported	OCD diagnosed in 10 (11.8%) cases and 2 (2.4%) controls ($\chi^2 = 5.73$; $p < 0.05$).
Shamsaei et al. (2015)	120 cases/100 controls (healthy individuals)	Cases: 34.5 (10.8) Controls: Not reported but described to be similar to cases	Cases: 71.7% Controls: Not reported but described to be similar to cases	Case-control, cross-sectional	McDonald criteria	SCL-90 obsessive-compulsive subscale	Not reported	Higher scores ($t = 3.76$; $p = 0.01$) in cases (1.31 ± 0.62) compared to controls (1.12 ± 0.57).
Uguz et al. (2008)	74 cases	34.57 (11.93)	67.6%	Cross-sectional	Poser criteria	SCID	N/A	OCD diagnosed in 11 (14.9%) cases.
Weisbrot et al. (2014)	45 cases	15.33 (2.0)	64.5%	Cross-sectional	International Pediatric MS Study Group criteria	K-SADS-PL	N/A	OCD diagnosed in 1 (4%) case.

Abbreviations: AD autoimmune disease; DSM-IV Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; OCD obsessive-compulsive disorder; OCS obsessive compulsive symptoms; MINI Mini International Neuropsychiatric Interview; MS multiple sclerosis; N/A not applicable; SCID Structured Clinical Interview for DSM-IV; SCL-90 Symptom Checklist 90; SCL-90-R Symptom Checklist 90 revised.

et al., 2005) found no significant results. To date, no studies have investigated the potential link between MS and tic disorders.

3.5. Systemic lupus erythematosus

Six studies reported on the association between SLE and OCD (Table 3). One study (Lindal et al., 1995) compared women with SLE with women from a population birth cohort and found no differences in the rate of OCD. Four additional studies (Bachen et al., 2009; Radhakrishan et al., 2011; Slattery et al., 2004; Zuñiga and Vásquez, 2014) without control groups reported prevalence rates of OCD higher than expected in the general population (ranging from 5.3 to 32%). One further study that used the Y-BOCS and the Obsessive Compulsive Inventory – Revised reported at least 9% of 54 SLE cases had moderate or severe OCD symptoms (Maciel et al., 2016).

Based on the limited evidence, it is currently unclear if SLE is associated with OCD/OCS. We could not find any studies examining the association between SLE and tic disorders.

3.6. Inflammatory bowel disease

Five studies examined the relationship between IBD and OCD/OCS (Table 4). Two studies without control groups focusing on IBD reported rates of OCD of 2.8% (lifetime prevalence) (Walker et al., 2008) and 7.4% (point prevalence) (Tribbick et al., 2015). Three further studies used the LOI to report on severity of OCS in samples of IBD patients, compared to controls. Of these, one study (Bellini and Tansella, 1976) compared ulcerative colitis (UC) patients with duodenal ulcer patients and found significantly higher scores on the LOI resistance and interference scales of the UC group, but not in the LOI symptom or trait scales. Another study compared UC cases with controls affected by anxiety and did not find significant differences in the LOI scores between the groups (Rabavilas et al., 1980). A third study compared three groups of children with UC, Crohn's disease (CD), and cystic fibrosis and found that UC cases scored significantly higher on the LOI symptom and resistance scales than the CD cases (Burke et al., 1989), but no differences were found when the UC and the CD cases were compared to the non-autoimmune (cystic fibrosis) group of patients. We did not find studies examining the prevalence of tic disorders in patients with IBD.

Taken together, the evidence for the association between IBD and OCD/OCS is currently scarce and inconclusive.

3.7. Insulin-dependent diabetes mellitus

Five studies reported on the association between IDDM and OCD/OCS (Table 5). Three studies without control groups (Friedman et al., 1998; Popkin et al., 1988; Tung et al., 2015) found low rates (from 0 to 1%) of OCD in relatively small IDDM samples (n = 41–136). On the other hand, one study (Ilias et al., 2005) found that pregnant women with IDDM presented significantly higher OCS severity scores compared to healthy women with gestational diabetes, assessed with the Maudsley Obsessive-Compulsive Inventory (Hodgson and Rachman, 1977). Similarly, another study found that the LOI scores were significantly higher in IDDM cases than in healthy controls (Winocour et al., 1990). No data on the relationship between IDDM and tic disorders are available.

Given the limited number of studies and the mixed results of the available literature, no conclusions can be drawn regarding the relation between IDDM and OCD/OCS or tic disorders.

3.8. Other systemic autoimmune disorders

Nine studies reported on the association between systemic ADs (other than RF and SLE) and OCD/OCS (Table 6). In this group, only one study on systemic sclerosis without a comparison group addressed the frequency of OCD, reporting a current and lifetime prevalence of 2% (Baubet et al., 2011).

Three of five studies that used the SCL-90 to examine OCS reported significantly higher scores in patients with scleroderma (Angelopoulos et al., 2001), ankylosing spondylitis (Durmus et al., 2014), and Sjögren's syndrome (Drosos et al., 1989), compared to healthy controls. The latter study also found that patients with Sjögren's syndrome had significantly higher OCS scores than patients with solid malignant tumors. By contrast, two studies found no significant differences on the severity of OCS, also measured with SCL-90, in groups of patients with Behçet's disease (Borhani Haghighi et al., 2007) and rheumatoid arthritis (RA) (Hyphantis et al., 2006), compared to matched healthy controls and matched hospital staff controls, respectively.

In one study (Hyphantis et al., 2013) using the SCL-90 to assess severity of OCS in two groups of patients with RA and ankylosing spondylitis, scores were similar to those reported in general population samples (Derogatis and Melisaratos, 1983). Another study (Kotsis et al., 2012) compared the same RA sample to a group of patients with psoriatic arthritis and, again, scores in both groups were similar to those obtained by the general population (Derogatis and Melisaratos, 1983).

Another study (Seçkin et al., 2000) assessing OCS with the SCL-90 found no significant differences among four different groups of patients, including two groups with ADs (RA and ankylosing spondylitis), patients with fibromyalgia, and patients with degenerative osteoarthritis.

Based on the available studies, the evidence linking systemic ADs (other than RF and SLE) and OCD/OCS is currently weak, and non-existing for tic disorders.

3.9. Organ-specific autoimmune disorders

Eleven studies reported on the association between organ-specific ADs (other than MS, IBD, and IDDM) and OCD/OCS (Table 7).

Four studies examined the presence of OCD/OCS in thyroid autoimmune-related disorders (Chattopadhyay et al., 2012; Giynas Ayhan et al., 2014; Müssig et al., 2012; Placidi et al., 1998). In two studies looking at Hashimoto thyroiditis, one found a higher prevalence of OCD in the AD group, compared to healthy controls (Giynas Ayhan et al., 2014), while the second study (Müssig et al., 2012) found that the SLC-90-R scores of the AD group were in the normal range. In two Graves's disease studies, results were also mixed. One study (Placidi et al., 1998) found a higher prevalence of OCD in the AD group, compared to patients with non-autoimmune thyroid disorders. Conversely, the other study (Chattopadhyay et al., 2012) did not find differences in the presence of OCD when comparing patients with Grave's disease with matched controls.

Of the six studies that explored skin-related ADs, three were on alopecia areata (AA) (Chu et al., 2012; Colon et al., 1991; Ghanizadeh, 2008), two on psoriasis (Hardy and Cotterill, 1982; Mehta and Malhotra, 2007), and one on vitiligo (Moretti et al., 2012). One register-based study (Chu et al., 2012) found an increased crude risk of OCD in cases with AA compared to matched controls (OR = 1.72, 95% CI = 1.06–2.77) that lost significance when adjusted for several possible confounders. Another study found a lifetime prevalence of OCD of 3% in AA patients (Colon et al., 1991). However, the last AA study (Ghanizadeh, 2008) reported presence of OCD in 35.7% of a sample of 14 children with AA. One study (Mehta and Malhotra, 2007) found no significant differences on the prevalence of OCD between a group of patients with psoriasis and a group of patients with chronic urticaria. Another study (Hardy and Cotterill, 1982) that used the LOI-CV to assess severity of OCS symptoms between patients with psoriasis, body dysmorphic disorder, and healthy matched controls, found that both clinical groups

Table 3
Studies examining the link between Systemic Lupus Erythematosus and OCD/OCS.

Study author (year)	Sample size n	Age mean (sd)	Gender % females	Study design	AD assessment	OCD/OCS assessment	Assessors blind to AD status	OCD outcomes
Bachen et al. (2009)	326 cases	47.9 (11.3)	100%	Cross-sectional	Medical chart review	CIDI	N/A	Lifetime OCD diagnosed in 8.9% [95% CI = 5.8–12.0] cases. Age-adjusted prevalence of OCD: 8.5% [95% CI = 5.5–11.5].
Lindal et al. (1995)	62 cases/421 controls (population group from a psychiatric epidemiological study)	Cases: 49.3 (16.2) Controls: Not reported	Cases: 100% Controls 100%	Case-control, cross-sectional	SLE present if any 4 of 11 ARA criteria were present	DIS- IIIA	Not reported	OCD diagnosed in 1.6% of the cases and 2.1% of the controls (not significant difference).
Maciel et al. (2016)	54 cases	Range 18–55	88.9%	Cross-sectional	American College of Rheumatology criteria	OCI-R, Y-BOCS	N/A	15 (27.8%) cases had abnormal OCI-R scores (≥21). 5 (9.3%) cases had moderate or severe symptoms on the Y-BOCS.
Radhakrishan et al. (2011)	100 cases (inpatients)	Range 18–60	Not reported	Cross-sectional	Not reported. Severity assessed with the Lupus Erythematosus Disease Activity Index (SLEDA) score	SCID	N/A	OCD diagnosed in 12 (12%) cases.
Slattery et al. (2004)	50 cases	42.1 (11.1)	90%	Cross-sectional	American College of Rheumatology criteria	Semi-structured clinical interview by a psychiatrist or psychiatrist clinical nurse and OCD self-report questionnaire	N/A	OCD diagnosed in 16 (32%) cases. Subclinical OCD in 5 (10%) further cases.
Zuñiga and Vásquez (2014)	38 cases	12.5 (2.4)	80%	Cross-sectional	American College of Rheumatology criteria	Not reported	N/A	OCD diagnosed in 2 (5.3%) cases.

Abbreviations: AD autoimmune disease; CIDI Composite International Diagnostic Interview; DIS-IIIA Diagnostic Interview Schedule; OCD obsessive-compulsive disorder; OCI-R Revised Obsessive and Compulsive Inventory; N/A not applicable; OCI-RSCID Structured Clinical Interview for DSM-IV; SLE systemic lupus erythematosus; Y-BOCS Yale-Brown Obsessive Compulsive Scale.

Table 4
Studies examining the link between Inflammatory Bowel Disease and OCD/OCS.

Study author (year)	Sample size n	Age mean (sd)	Gender % females	Study design	AD assessment	OCD/OCS assessment	Assessors blind to AD status	OCD/OCS outcomes
Bellini and Tansella (1976)	30 UC cases/30 controls (duodenal ulcer patients)	Cases: 33.17 (10.1) Controls: 44.07 (12.1)	Cases: 26.7% Controls: 66.7%	Case-control, cross-sectional	Rectal biopsies, barium enema, proctosigmoidoscopy, and stool examinations	LOI	Not reported	Significant differences in LOI resistance ($p < 0.0001$) and LOI interference ($p = 0.05$) between cases (18.7 and 26.5, respectively) and controls (7.5 and 10, respectively). When analyses were separated by sex, differences in interference were not significant in women.
Burke et al. (1989)	44 cases (33 CD + 11 UC)/46 controls (cystic fibrosis patients)	CD: 13.62 (2.75) UC: 11.18 (2.36) Cystic fibrosis: 12.6 (2.10)	Not reported	Case-control, cross-sectional	Not reported. Severity rated by the Lloyd-Still and Green Scales	LOI-CV	Not reported	Significant differences between groups in the LOI-CV 'yes' scale ($F = 5.21$, $p = 0.007$). UC scores were higher than CD scores ($p < 0.05$), but similar to cystic fibrosis scores. CD and cystic fibrosis scores did not differ. Same pattern for the LOI-CV resistance scores ($F = 3.27$; $p = 0.04$; differences between UC and CD groups were significant, $p > 0.05$). Interference scores did not differ between groups ($F = 1.89$, $p = 0.16$).
Rabavilas et al. (1980)	15 UC cases/15 controls (age- and sex-matched anxiety patients)	Cases: 35.6 (10.6) Controls: 36.2 (9.6)	Cases: 53.3% Controls: Not reported but matched	Case-control, cross-sectional	Not reported	LOI	Not reported	Non-significant differences in LOI traits score between cases (13.20 ± 3.39) and controls (11.20 ± 3.50).
Tribbick et al. (2015)	81 cases	35.07 (12.51)	51.9%	Cross-sectional	Not reported	MINI	N/A	OCD diagnosed in 6 (7.4%) cases.
Walker et al. (2008)	351 cases (48% CD + 46% UC + 6% indeterminate colitis)	43 (14.06)	60%	Cross-sectional, population-based	Not reported	CIDI	N/A	Lifetime OCD diagnosed in 10 (2.8%) cases.

Abbreviations: AD autoimmune disease; CD Crohn's disease; CIDI Composite International Diagnostic Interview; IBD inflammatory bowel disease; ICD-9 The International Classification of Diseases, Ninth Revision; LOI-CV Leyton Obsessional Inventory Child version; LOI Leyton Obsessional Inventory; OCD obsessive-compulsive disorder; OCS obsessive compulsive symptoms; MINI Mini International Neuropsychiatric Interview; N/A not applicable; NAIMs no autoimmune markers; UC ulcerative colitis.

Table 5
Studies examining the link between Insulin Dependent Diabetes Mellitus and OCD/OCS.

Study author (year)	Sample size n	Age mean (sd)	Gender % females	Study design	AD assessment	OCD/OCS assessment	Assessors blind to AD status	OCD/OCS outcomes
Friedman et al. (1998)	41 cases	27.2 (8.8)	46.34%	Cross-sectional	Not reported	SADS-LA R	N/A	No cases of OCD were observed.
Ilias et al. (2005)	23 cases (pregnant women)/13 controls (healthy women with gestational diabetes)	Cases: 29.5 (4.1) Controls: 28.9 (3.5)	Cases: 100% Controls: 100%	Case-control, cross-sectional	Laboratory assessment	MOCI	Not reported	Higher MOCI scores in cases than in controls both in the 2nd (14.4 ± 2.8 vs 9 ± 3.5) and 3rd (14.9 ± 6.3 vs 9.3 ± 6.8 vs) trimesters of pregnancy (both $p < 0.05$).
Popkin et al. (1988)	75 cases (transplant candidates)	Cases: 31 (range 16–55)	Cases: 64%	Cross-sectional	A 10-year course of IDDM nephropathy with albuminuria >30 mg/d and abnormal biopsy results	DIS	N/A	OCD diagnosed in 1 (1.3%) case.
Tung et al. (2015)	136 cases	39.8 (12.1)	55%	Cross-sectional	Clinical assessment	SCID	N/A	OCD diagnosed in 1 (0.7%) case.
Winocour et al. (1990)	130 cases/155 controls (healthy individuals)	Cases: 40.3 Controls: Not reported	Cases: 36.15% Controls: 48.39%	Case-control, cross sectional	Full physical examination and laboratory assessment	LOI	Not reported	Obsessional traits significantly higher ($p < 0.01$) in cases (16.1 ± 0.7) than in controls (9.1 ± 0.9).

Abbreviations: AD autoimmune disease; DIS diagnostic interview schedule; IDDM insulin dependent diabetes mellitus; LOI Leyton Obsessional Inventory; OCD obsessive-compulsive disorder; OCS obsessive compulsive symptoms; MOCI Maudsley Obsessional-Compulsive Inventory; SADS-LA R Schedule for Affective Disorders and Schizophrenia–Lifetime version–modified for the study of anxiety disorders; SCID Structured Clinical Interview for DSM-IV

Table 6
Studies examining the link between other Systemic Autoimmune Disorders (other than RF and SLE) and OCD/OCS.

Study author (year)	Sample size n	Age mean (sd)	Gender % females	Study design	AD assessment	OCD/OCS assessment	Assessors blind to AD status	OCD/OCS outcomes
Angelopoulos et al. (2001)	30 scleroderma cases/33 controls (healthy individuals)	Cases: 46.4 Controls: 49.8	100%	Case-control, cross-sectional	American College of Rheumatology criteria	SCL-90-R obsessive-compulsive subscale	Not reported	Higher scores ($p = 0.0004$) in cases (0.73 ± 0.54) compared to controls (0.34 ± 0.35).
Baubet et al. (2011)	100 SSc cases	53 (range 44–60)	86%	Cross-sectional	American Rheumatism Association and/or Leroy & Medsger criteria	MINI	N/A	Current OCD diagnosed in 2 (2%) cases. Lifetime OCD diagnosed in 2 (2%) cases.
Borhani Haghighi et al. (2007)	64 BD cases/65 controls (age-, gender-, and education-matched healthy individuals)	Cases: 36.2 (8.9) Controls: Not reported (but matched)	Cases: 62.5% Controls: Not reported (but matched)	Case-control, cross-sectional	International Study Group (ISG) criteria for Behçet's disease	SCL-90-R obsessive-compulsive subscale	Not reported	Similar scores ($p = 0.31$) in cases (11.3 ± 8.3) and controls (9.9 ± 7.3).
Drosos et al. (1989)	33 SS/41 clinical controls (solid malignant tumor patients)/33 general population controls (healthy individuals)	Not reported	100%	Case-control, cross-sectional	Positive minor salivary gland biopsy (score ≥ 2, according to Tarpley's classification)	SCL-90-R obsessive-compulsive subscale	Not reported	Higher scores ($p = 0.019$) in SS compared to general population controls. Higher scores ($p = 0.038$) in SS compared to clinical controls. No significant differences between clinical and general population controls.
Durmus et al. (2014)	80 AS cases/80 controls (matched healthy individuals)	Cases: 39.33 (10.98) Controls: 36.41 (10.84)	Cases. 36.2% Controls: 28.8%	Case-control, cross-sectional	Modified New York criteria, Bath Ankylosing Spondylitis Disease Activity Index, and Bath Ankylosing Spondylitis Functional Index	SCL-90-R obsessive-compulsive subscale	Not reported	Higher scores ($p > 0.013$) in cases (0.85 ± 0.77) compared to controls (0.47 ± 0.44).
Hyphantis et al. (2006)	22 RA cases/34 controls (matched hospital staff individuals)	Cases: 51.0 (14.6) Controls: 46.1 (12.4)	Cases: 72.7% Controls: 73.5%	Case-control, cross-sectional	American College of Rheumatology criteria	SCL-90-R obsessive-compulsive subscale	Not reported	Similar scores (no significant differences) in cases (1.2 ± 0.6) and controls (0.9 ± 0.5).
Hyphantis et al. (2013)	199 RA cases/55 AS cases	RA: 55.2 (13.6) AS: 42.9 (10.9)	RA: 82.4% AS: 14.5%	Cross-sectional	AS: Modified New York criteria RA: American College of Rheumatology criteria	SCL-90-R obsessive-compulsive subscale	N/A	Similar scores ($F = 0.920$; $p = 0.338$) in AS (0.81 ± 0.12) and RA (0.68 ± 0.05) cases.
Kotsis et al. (2012)	83 PsA cases/199 RA cases	PsA cases: 48.9 (12.4) RA cases: 55.2 (13.7)	PsA cases: 47.0% RA cases: 82.4%	Cross-sectional	PsA: Classification of Psoriatic Arthritis Study Group criteria RA: American College of Rheumatology criteria	SCL-90 obsessive-compulsive subscale	N/A	Similar scores ($F = 0.390$; $p = 0.533$) in PsA (0.74 ± 0.09) and RA (0.67 ± 0.05) cases.
Seçkin et al. (2000)	21 RA cases/28 AS cases/24 fibromyalgia controls/28 DA controls	RA: 42.6 (15.2) AS: 35.1 (11.2) Fibromyalgia: 38 (10.5) DA: 55.8 (15.3)	Not reported	Cross-sectional	Not reported	SCL-90-R obsessive-compulsive subscale	Not reported	Similar scores (no significant differences) between RA (17 ± 6.1), AS (18.7 ± 19.6), fibromyalgia (13.3 ± 5.8), and DA (11.1 ± 6) scores.

Abbreviations: AD autoimmune disease; AS ankylosing spondylitis; BD Behçet's disease; DA degenerative osteoarthritis; FM fibromyalgia; MINI Mini International Neuropsychiatric Interview; N/A not applicable; OCD obsessive-compulsive disorder; OCS obsessive compulsive symptoms; PsA Psoriatic arthritis; RA rheumatoid arthritis; SCL-90 Symptom Checklist 90; SCL-90-R Symptom Checklist 90 revised; SS Sjögren's syndrome; SSc systemic sclerosis.

Table 7
Studies examining the link between Other Organ-Specific Autoimmune Disorders (other than MS, IBD, and IDDM) and OCD/OCS.

Study author (year)	Sample size n	Age mean (sd)	Gender % females	Study design	AD assessment	OCD/OCS assessment	Assessors blind to AD status	OCD/OCS outcomes
Obsessive-Compulsive Disorder/Obsessive-Compulsive Symptoms in Thyroid-Targeted Autoimmune Disorders								
Chattopadhyay et al. (2012)	36 GD cases/30 controls (age- and sex-matched individuals)	Cases: 35.8 (5) Controls: 36.3 (6.5)	Cases: 88.9% Controls: Not reported (but matched)	Case-control, cross-sectional	Clinical examinations, T3, T4, TSH levels, and anti-TPO levels	Psychiatric interview based on DSM-IV criteria	Yes	OCD was diagnosed in 6 (16.67%) cases and 1 (3.3%) control ($\chi^2 = 3.068$; $p = 0.080$).
Giynas Ayhan et al. (2014)	51 euthyroid HT cases/45 euthyroid goiter controls/68 controls (healthy individuals)	Euthyroid HT: 35.10 (7.75) Euthyroid goiter: 35.47 (6.74) Controls: 33.82 (6.07)	Euthyroid HT: 96.1% Euthyroid goiter: 91.1% Controls: 94.1%	Case-control, cross-sectional	Hypoechogenic pattern in ultrasound and high titers of anti-Tg and anti-TPO + normal serum levels of FT3/FT4 and TSH	SCID	Not reported	OCD was diagnosed in a greater proportion in the HT group compared to the healthy individuals group ($p = 0.005$). No significant differences were found between the HT and the goiter group.
Müssig et al. (2012)	64 HT cases	46 (11)	88%	Cross-sectional	Hypoechogenic pattern ultrasound. Previous high levels of anti-TPO and/or anti-Tg	SCL-90-R obsessive-compulsive subscale	N/A	SCL-90-R scores were within the normal range although significantly higher in HT cases with positive anti-TPO than negative anti-TPO ($p = 0.015$).
Placidi et al. (1998)	47 GD cases/46 controls (individuals with other thyroid diseases)	48.2 (13.7)	Cases: 80.85% Controls: 73.91%	Case-control, cross-sectional	The endocrinologists reviewed all thyroid function test abnormalities and classified the patients	SCID-UP-R	Not reported	OCD was diagnosed in 5 (10.6%) cases and 0 controls ($\chi^2 = 6.32$; $p = 0.012$).
Obsessive-Compulsive Disorder/Obsessive-Compulsive Symptoms in Skin- Targeted Autoimmune Disorders								
Chu et al. (2012)	5117 AA cases/20,468 controls (matched population individuals)	0–19: 17.7% 20–39: 52.5% 40–59: 25.3% ≥60: 4.4%	50.8%	Case-control, cross-sectional, register-based	Diagnosis by a dermatologist based on ICD-9 criteria	Diagnosis by a psychiatrist based on ICD-9 criteria	No	OCD diagnosed in 24 (0.5%) cases and 56 (0.3%) controls (crude OR = 1.72, 95% CI = 1.06–2.77; OR adjusted for age, sex, income, geographical location and other psychological diseases = 1.58, 95% CI = 0.96-2.60.
Colon et al. (1991)	31 AA cases	35 Range: 17–59	71%	Cross-sectional	Not reported	DIS	N/A	Lifetime OCD diagnosed in 1 (3%) case.
Ghanizadeh (2008)	14 AA cases	11.66 (6.08)	Not reported	Cross-sectional	Not reported	K-SADS-PL	N/A	OCD diagnosed in 5 (35.7%) cases.

Table 7 (*Continued*)

Study author (year)	Sample size n	Age mean (sd)	Gender % females	Study design	AD assessment	OCD/OCS assessment	Assessors blind to AD status	OCD/OCS outcomes
Hardy and Cotterill (1982)	11 psoriasis cases/12 clinical controls (patients with dysmorpho-phobia)/12 general population controls (matched individuals)	Cases: 40.4 (13.2) Clinical controls: 42.3 (12.7) General population controls: 42.6 (11.3)	Cases: 81.82% Clinical controls: 83.33% General population controls: Not reported (but matched)	Case-control, cross-sectional	Not reported	LOI-CV	Not reported	Higher OCS scores ($p < 0.001$) in cases (22.5 ± 4.9) and clinical controls (21.8 ± 7.4), compared to general population controls (8.8 ± 5.0). No differences reported between cases and clinical controls.
Mehta and Malhotra (2007)	50 psoriasis cases/50 controls (chronic urticarial patients)	Cases: 37.98 (12.84) Controls: 36.30 (13.25)	Cases: 14% Controls: 56%	Case-control, cross-sectional	Dermatological examination	MINI	Not reported	OCD diagnosed in 0cases and 1 (2%) controls (no significant differences).
Moretti et al. (2012)	56 non-segmental vitiligo cases with autoimmune markers (AIMs)/56 controls (matched non-segmental vitiligo individuals without autoimmune markers [NAIMs])	Cases: 36.9 (16.4) Controls: 36.4 (15.9)	Cases: 66.07% Controls: 66.07%	Case-control, cross-sectional	Medical history and physical exam using a modified Vitiligo European Task Force (VETF) form	MHQ	Not reported	Higher OCS scores ($p = 0.000$) in cases compared to controls. High MHQ scores were significantly predictive of AIMs and low MHQ scores were significantly predictive of NAIMs.
Obsessive-Compulsive Disorder in Muscle- Targeted Autoimmune Disorders								
Ybarra et al. (2011)	41 MG cases	37.4 (13.4)	78.1%	Cross-sectional	Laboratory and electromyography assessment	MINI-Plus	N/A	OCD diagnosed in 4 (9.8%, 95% CI = 0.7%-18.8%) cases.

Abbreviations: AA alopecia areata; AD autoimmune disease; AIMs autoimmune markers; DIS diagnostic interview schedule; DSM-IV Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; GD Grave's disease; HT Hashimoto thyroiditis; K-SADS-PL Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime; ICD-9 The International Classification of Diseases, Ninth Revision; LOI-CV Leyton Obsessional Inventory Child version; LOI Leyton Obsessional Inventory; OCD obsessive-compulsive disorder; OCS obsessive compulsive symptoms; OR Odds Ratio; MG myasthenia gravis; MHQ Middlesex Hospital Questionnaire; MINI Mini International Neuropsychiatric Interview; N/A not applicable; NAIMs no autoimmune markers; SCID Structured Clinical Interview for DSM-IV; SCID-UP-R Structural Clinical Interview for DSM III-R Upjohn-version; SCL-90 Symptom Checklist 90; SCL-90-R Symptom Checklist 90 revised.

scored significantly higher than the healthy controls. Finally, one study (Moretti et al., 2012) found that a group of patients with vitiligo with autoimmune markers reported significantly higher scores on the obsessive-compulsive traits and symptoms subscale of the Middlesex Hospital Questionnaire (Crown and Crisp, 1966) than a group of patients with vitiligo without autoimmune markers. One further study (Ybarra et al., 2011) reported an OCD rate of 9.8% in 41 cases of myasthenia gravis, a muscle-target AD.

According to the available evidence, the potential link between organ- specific ADs and OCD/OCS is inconclusive and comes from generally small clinical samples (n = 11-64), with the exception of a study that used an epidemiological sample of 5117 AA cases compared to 20,468 controls (Chu et al., 2012). Of note, that study found that the adjusted risk of OCD among AA cases was 1.58 (95% CI = 0.96-2.60) compared to controls. Data relating organ-specific ADs (other than MS, IBD, and IDDM) and tic disorders are unavailable.

3.10. Autoimmune diseases in OCD or tourette's disorder

There have been no studies systematically examining the prevalence of ADs in samples of OCD or tic disorder patients. However, three studies with small sample sizes (n = 9–21) examined the presence of antibodies associated with autoimmunity in individuals with TD (Table 8). Two clinic-based case-control studies (Singer et al., 1997; Toren et al., 1994) measured the occurrence of antiphospholipid autoantibodies (APA) in TD cases and found little support for a meaningful association. In another study (Dua et al., 2014), the serum from four out of 21 children diagnosed with TD was found positive when analyzed for antibodies against the presence of N-methyl-D-aspartate receptor (NMDAR).

In sum, the available evidence of the association between ADs and tic disorders is also inconclusive when participants are selected on the basis of their tic disorder status.

3.11. Family-based studies

Five family-based studies explored the association between ADs and OCD and/or tic disorders (Table 9). Two examined mothers of individuals with OCD/tic disorders (Murphy et al., 2010) or TD (Dalsgaard et al., 2015) and three studies examined mothers (Burke et al., 1994) and first degree relatives of individuals with an AD (Hounie et al., 2007; Seixas et al., 2008). Burke et al. (1994) found no significant differences in the rates of OCD in mothers of children and adolescents with IBD, compared to the mothers of children and adolescents with cystic fibrosis (a non-autoimmune genetic disease). Another study (Murphy et al., 2010) without a control group examined the biological mothers of children with OCD and/or tic disorders and found that 17.8% had an AD, which is a higher proportion than would be expected among women in the general population (approximately 5%) (Cooper and Stroehla, 2003). Among the individual ADs examined, the proportion of mothers with SLE was significantly higher than expected in the general population (Jacobson et al., 1997). On the other hand, the prevalence of IDDM was significantly lower in the mothers of children with OCD, compared to what would be expected in the general population (Dray-Spira et al., 2008).

A longitudinal population-based study showed that the risk of TD in the offspring of mothers with 31 different ADs was about 22% higher than in the general population (Dalsgaard et al., 2015). The most common maternal ADs were UC, RA, thyrotoxicosis, and MS, although power was limited to examine the risk for many of the individual ADs (Dalsgaard et al., 2015). In two case-control family studies that analyzed the same Brazilian sample with different statistical approaches (Hounie et al., 2007; Seixas et al., 2008), the rate of obsessive-compulsive spectrum disorders, including OCD and tic disorders, was significantly higher among first degree relatives of individuals with RF (of whom 28 had SC and 31 did not) than among first degree relatives of controls.

Thus, there is some preliminary evidence to suggest that ADs and OCD/tic disorders may co-aggregate in families but the available studies have been generally underpowered to examine the association with individual ADs and require replication.

4. Discussion

In an attempt to summarize a large and disperse literature, we conducted the first systematic review of the potential link between ADs and OCD/tic disorders. The results suggested associations between some ADs, particularly RF co- occurring with SC, and OCD/OCS. For tic disorders, the reported association with ADs is largely anecdotal and mainly limited to RF. There is some preliminary evidence that ADs and OCD/OCS and tic disorders may co-aggregate in families, suggesting possible genetic and/or environmental associations between these disorders. However, the conclusions of our review are severely limited by both the scarcity of research studies and methodological issues. The latter included the recruitment of small sample sizes mainly from specialist clinics, the use of cross-sectional designs, lack of blind assessors, lack of control groups, and the use of self-report measures known to have poor psychometric properties) (Stewart et al., 2005; Woody et al., 1995). For example, almost all of the eligible studies (97%) included in our systematic review used a cross-sectional design, which might have introduced different types of bias, such as reporting bias (patients or health professionals may be more likely to give additional diagnoses to patients that already have one), measurement bias (given the hypothesized association, patients or providers may be more likely to screen for both conditions), or confounding by a third factor (having both OCD/tic disorders and an ADs may be associated with more frequent medical appointments, increasing the likelihood of a double diagnosis).

For these reasons, we propose that, at this stage, this putative association should be studied further by conducting larger controlled or population- based studies, using appropriate assessment methods and longitudinal designs in order to minimize biases. These studies would be optimally conducted by multidisciplinary teams that include expertise in both immunology and mental health sciences (many of the studies reviewed above were conducted by specialists in ADs).

4.1. Future directions

In order to confirm the potential association that may exist between at least some ADs and OCD/tic disorders, we propose the implementation of a range of complementary study designs, each with their own strengths and limitations:

1. *Case-control studies of well characterized patients with an AD and matched controls*. Sample sizes should be sufficiently powered to detect disorders of modest prevalence such as OCD and tic disorders. OCD and tic disorders should be diagnosed via validated semi-structured interviews (which were not used in almost a third of the reviewed studies reporting categorical outcomes) and raters should be blind to the participants' AD or control status (a condition that was only met in about one fifth of all case-control studies included in this review). Additionally, symptom severity should be ascertained via both clinician (Y-BOCS) and self-rated instruments with sound psychometric properties. In the reviewed literature, a large number of studies focusing on OCS employed the obsessive-compulsive scale of the SCL-90 (52%) or the LOI (36%), which are widely regarded as sub-optimal

Table 8
Studies that examine antibodies associated with autoimmunity in individuals with TD.

Study author (year)	Sample size n	Age mean (sd)	Gender % females	Study design	Autoimmunity assessment	Tic disorders assessment	Assessors blind to AD status	ADs outcomes
Dua et al. (2014)	21 TD cases assessed for the presence of anti-NMDAR receptor encephalitis	11	Not reported	Cross-sectional	Sera analyzed using HEK293 cells transfected with NR1:NR2B subunits and co-transfected with enhanced green fluorescent protein (EGFP)	Not reported	N/A	Antibodies anti-NMDAR in 4 (19%) cases.
Singer et al. (1997)	21 TD cases/20 controls (outpatient clinic individuals) assessed for the presence of APS	Cases: 11.0 (2.7) Controls: 11.8 (2.8)	Cases: 14.29% Controls: 30%	Case-control, cross-sectional	Laboratory assessment of lupus anticoagulant, anticardiolipin (aCL), antibodies and antinuclear antibodies	TD as defined by the Tourette Syndrome Classification Group	Not reported	aCL IgG antibody levels, assayed in 19 of the 21 subjects, were normal in 16 children and low positive in 3. In the 20 non-TD clinic controls, aCL IgG levels were normal in 18, and two had low positive values. aCL IgM and IgA antibody levels were normal in all patients with TD. Clinically, there was no difference between the groups with normal and low positive IgG levels.
Toren et al. (1994)	9 TD cases/9 healthy controls assessed for the presence of APS	12 (1.8)	Not reported	Case-control, cross-sectional	Laboratory assessment	Based on DSM-III-R criteria	Not reported	Antiphospholipid antibodies in 4 (44.4%) cases and 0 controls.

Abbreviations: AD autoimmune disease; APS antiphospholipid syndrome NMDAR *N*-methyl D- aspartate receptor; DSM-III-R Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition revised; TD Tourette's disorder.

Table 9
Family studies examining the link between Autoimmune Disorders and OCD or tic disorders.

Study author (year)	Sample size n	Age mean (sd)	Gender % females	Study design	AD assessment	OCD or tic disorders assessment	Assessors blind to AD status	ADs or OCD or tic disorders outcomes
Burke et al. (1994)	72 mothers of children and adolescents with IBD (cases)/44 mothers of children and adolescents with CF (controls)	Cases: 39.5 (5.12) Controls: 37.2 (6.15)	100	Case-control, cross-sectional	Mothers explored for IBD (CD or UC) via a clinical assessment	A-SADS	Not reported	Lifetime OCD diagnosed in 5 IBD (2 with UC/3 with CD) and 0 CF mothers ($X^2 = 1.78$; $p = 0.1$).
Dalsgaard et al. (2015)	2442 TD children/1,113,813 controls (children from the general population)	Not reported	16.9%	Cohort study, register-based	Mothers explored for any autoimmune disorder via a clinical assessment	Register-based on ICD-8/ICD-10 diagnostic criteria	No	Increased risk of TD in children of mothers with history of ADs (IRR = 1.22, 95% CI = 1.01–1.48; p = 0.048) (males TD: IRR = 1.29, 95% CI = 1.05–1.58; females TD: 0.89, 95% CI = 0.52-1.52).
Hounie et al. (2007)	59 children (28 with RF + SC and their 120 first-degree relatives; 31 RF-SC and their 131 first-degree relatives)/39 controls	Cases: 14.36 (4.60) Controls: 11.51 (3.29)	Cases: 55.9% Controls: 38.5%	Case-control, cross-sectional	First-degree relatives explored for Antistreptolysin O (ASO) titers	K-SADS-E (relatives under 18), SCID (adult relatives)	Yes	Diagnosis of OCSDs (including OCD, tic disorders, BDD and pathologic 'grooming' habits –TTM, pathologic onychophagia and skin picking) in 37 (14.7%) first-degree relatives of cases and 10 (7.3%) first- degree relatives of controls (p = 0.028).
Murphy et al. (2010)	107 biological mothers of children with OCD and/or tics	38.33 (4.86)	100%	Cross-sectional	Mothers explored for any autoimmune disorder via a clinical assessment	K-SADS	N/A	ADs diagnosed in 18 (17.8%) mothers of children with OCD and/or tics.
Seixas et al. (2008)	59 children (28 with RF + SC and their 120 first-degree relatives; 31 RF-SC and their 131 first-degree relatives)/39 controls	Cases: 14.36 (4.60) Controls: 11.51 (3.29)	Cases: 55.9% Controls: 38.5%	Case-control, cross-sectional	First-degree relatives explored for Antistreptolysin O (ASO) titers	K-SADS-E (relatives under 18), SCID (adult relatives)	Yes	Frequency of OCSDs (including OCD, CTD, TD, transient tic disorders and BDD) was higher in RF probands than in control probands. The risk of tic disorders, OCD, or BDD (at least one present in a single individual) was elevated by the presence (in another family member) of RF (p = 0.0033) or SC (p = 0.0307).

Abbreviations: AD autoimmune disease; BDD body dysmorphic disorder; CD Crohn's disease; IBD inflammatory bowel disease; IRR incidence rate ratio; CF cystic fibrosis; ICD-8 The International Classification of Diseases, Eighth Revision; ICD-10 The International Classification of Diseases, Tenth Revision; K-SADS Schedule for Affective Disorders and Schizophrenia for School-Age Children; KSADS-E Schedule for Affective Disorders and Schizophrenia for School-Age Children—Epidemiologic Version; OCD obsessive-compulsive disorder; OCSD obsessive compulsive spectrum disorders; RF rheumatic fever; A-SADS Adults Schedule for Affective Disorders and Schizophrenia, Lifetime version; SC Sydenham's chorea; SCID Structured Clinical Interview for DSM-IV; TD Tourette's disorder; TTM trichotillomania; UC ulcerative colitis.

measures of OCS (Stewart et al., 2005; Woody et al., 1995). While valuable, these kinds of studies would still be affected by limitations such as the reliance on samples from specialist clinics and cross-sectional designs.

2. *Population-based cohort studies*. In this systematic review, all eligible studies except for two (Chu et al., 2012; Dalsgaard et al., 2015) included samples recruited from specialist clinics. In order to minimize potential confound associated with this selection bias, we propose the use of large-scale population based cohorts, ideally with national coverage. Birth cohorts, such as those available in the Nordic countries, allow the use of prospectively collected health data and the control of a wide range of confounders. Given the substantial psychiatric comorbidity rates of both OCD and tic disorders with other neuropsychiatric disorders (March and Leonard, 1996; Robertson, 2015), the potentially confounding effect of psychiatric comorbidities should be explored; this will minimize the risk that the ADs are associated with a comorbid condition rather than OCD/tic disorders themselves. It is also possible that ADs are non-specifically associated with a wide range of mental disorders, which would also be informative, as it would suggest a potential transdiagnostic mechanism. This is plausible since ADs have been frequently associated with psychiatric disorders other than OCD and tic disorders (Atladottir et al., 2009; Benros et al., 2013; Carta et al., 2004; Eaton et al., 2006). Thus, future studies could include individuals with a range of psychiatric disorders, as well as medical controls and healthy individuals, in order to test the specificity of the association between ADs and OCD and tic disorders.
3. *Controlled or population-based family studies.* Overall, the results of the family studies reviewed above provide preliminary support for the hypothesis that immunological factors may play a role in the etiology of at least some individuals with OCD and/or tic disorders. These results require confirmation in either controlled (clinic-based) family studies (employing blind psychiatric evaluations) or population- based family studies. With sufficiently large sample sizes, these kind of studies would also offer the opportunity to further understand the nature of the relation between ADs and OCD/tic disorders by attempting to tease apart genetic from environmental risk factors. One possibility is that ADs and OCD/tic disorders share genetic risk factors (Hounie et al., 2008). To test this hypothesis, family studies examining rates of ADs in relatives of OCD/tic disorder patients (or vice versa) with various degrees of relatedness to the probands (e.g., comparing the risks in first, second, and third degree relatives) would be informative. If the shared genetic risk hypothesis were correct, we would expect that the risks for first degree relatives would be higher than those for second and third degree relatives. An alternative, not mutually exclusive possibility is that mothers transmit antibodies to their offspring via the placenta (Lee et al., 2009; Palmeira et al., 2012). If this were correct, we would expect a significantly higher risk of ADs in mothers than in fathers – or other first- degree relatives – of patients with OCD/tic disorders.

Each of the above study designs have their own limitations but if the results of these kinds of studies are replicated and converge to support the same conclusions, the hypothesis that at least some patients with OCD or tic disorders have an immunological component will be strengthened considerably. Studies aimed at understanding the mechanisms that lead to this association will be warranted. For instance, through gene-searching studies in OCD/tic disorders that focus on certain genetic variants that are already known to be involved in autoimmune diseases (Barrett et al., 2009; Hafler et al., 2007; Hugot et al., 2001; Stahl et al., 2010), or studies investigating the activation of the immune system in the serotoninergic/dopaminergic/glutamatergic neurotransmission at the cortico- striato-thalamo-cortical circuits (e.g., anti-basal ganglia auto-antibodies, distinct cytokine profiles or other potential biomarkers) (Dale and Brilot, 2012; Gray and Bloch, 2012; Hoekstra and Minderaa, 2005; Martino et al., 2009; Parker-Athill et al., 2015; Pearlman et al., 2014).

This information would also have important implications for clinical practice, since it would motivate screening for ADs in patients with OCD/tic disorders and their relatives, and potentially lead to novel pharmacological therapies based on immune regulation in patients who have an immunological component.

It is worth noting that if these studies converged to conclude that there is no clear comorbidity or familial co-aggregation between ADs and OCD/tic disorders, we may still not be able to fully rule out the possibility of altered immunological processes in a small subgroup of OCD/tic patients. However, the hypothesis that AD and OCD/tics share some genetic or environmental risk factors would be considerably weakened.

4.2. Limitations

This systematic review is not without limitations. The weight of RF in the eligible studies, compared to other ADs, may have introduced a bias in the results, leading to the conclusion that this AD is specifically associated to OCD, unlike other ADs where the literature is scarcer. Though we deliberately excluded studies that examined ADs in PANDAS patients (by definition these patients have altered immunological processes), an unknown proportion of the studied OCD and/or tic disorder cases may have met criteria for PANDAS or PANS, therefore inflating the observed associations and familial links with ADs.

5. Conclusion

A positive association between some ADs and OCD/tic disorders appears to exist. However, most of the reviewed studies had methodological limitations that preclude firm conclusions at this stage. A number of possible research designs are available to help confirm or refute these associations and to elucidate their mechanisms.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neubiorev.2016.09.025.

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