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Review article

Thyroid autoimmunity in bipolar disorder: A systematic review

Margherita Barbuti[a,b], André F. Carvalho[c], Cristiano A. Köhler[c], Andrea Murru[a], Norma Verdolini[a,d], Giovanni Guiso[a], Ludovic Samalin[e], Michael Maes[f,g,h,i,j], Brendon Stubbs[k,l], Giulio Perugi[b], Eduard Vieta[a,*], Isabella Pacchiarotti[a]

[a] Bipolar Disorders Unit, Clinical Institute of Neurosciences, Hospital Clinic, IDIBAPS, University of Barcelona, CIBERSAM, Barcelona, Catalonia, Spain
[b] University of Pisa, Pisa, Italy
[c] Translational Psychiatry Research Group and Department of Clinical Medicine, Faculty of Medicine, Federal University of Ceara, Fortaleza, CE, Brazil
[d] Division of Psychiatry, Clinical Psychology and Rehabilitation, Department of Medicine, Santa Maria della Misericordia Hospital, University of Perugia, Perugia, Italy
[e] CHU Clermont-Ferrand, Department of Psychiatry, EA 7280, University of Auvergne, Clermont-Ferrand, France
[f] Department of Psychiatry, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
[g] IMPACT Strategic Research Center, School of Medicine, Barwon Health, Deakin University, Geelong, Australia
[h] Health Sciences Postgraduate Program, Health Sciences Center, State University of Londrina, Londrina, Brazil
[i] Revitalis, Waalre, The Netherlands
[j] Department of Psychiatry, Medical University of Plovdiv, Plovdiv, Bulgaria
[k] Physiotherapy Department, South London and Maudsley NHS Foundation Trust, Denmark Hill, London SE5 8AZ, United Kingdom
[l] Health Service and Population Research Department, Institute of Psychiatry, Psychology and Neuroscience, King's College London, De Crespigny Park, Box SE5 8AF, London, United Kingdom

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ABSTRACT

Background: Accumulating evidence points to the pathophysiological relevance between immune dysfunction and mood disorders. High rates of thyroid dysfunction have been found in patients with bipolar disorder (BD), compared to the general population. A systematic review of the relationship between BD and thyroid autoimmunity was performed.

Methods: Pubmed, EMBASE and PsycINFO databases were searched up till January 28th, 2017. This review has been conducted according to the PRISMA statements. Observational studies clearly reporting data among BD patients and the frequency of autoimmune thyroid pathologies were included.

Results: 11 original studies met inclusion criteria out of 340 titles first returned from the global search. There is evidence of increased prevalence of circulating thyroid autoantibodies in depressed and mixed BD patients, while there is no evidence showing a positive relationship between BD and specific autoimmune thyroid diseases. There is a controversy about the influence of lithium exposure on circulating thyroid autoantibodies, even if most of studies seem not to support this association. A study conducted on bipolar twins suggests that autoimmune thyroiditis is related to the genetic vulnerability to develop BD rather than to the disease process itself. Females are more likely to develop thyroid autoimmunity.

Limitations: The samples, study design and outcomes were heterogeneous.

Conclusion: Thyroid autoimmunity has been suggested to be an independent risk factor for bipolar disorder with no clear association with lithium exposure and it might serve as an endophenotype for BD.

1. Introduction

Recent emergent evidence points to the importance of the etiopathogenetic relationship between activation of immune-inflammatory pathways and psychiatric syndromes, including bipolar disorder (BD) (Berk et al., 2011; Grande et al., 2016; Hamdani et al., 2013; Leon-Caballero et al., 2015; Maes et al., 1995; Rege and Hodgkinson, 2013; Siwek et al., 2016). Available data support a relationship between autoimmunity and BD. For example, BD patients have significantly more and higher autoantibodies (autoAbs) compared with healthy controls and other psychiatric patients (Sidhom et al., 2012). A large cohort study reported that non-specific autoimmune processes could precede the onset of BD (Eaton et al., 2010). Furthermore, it is quite known that certain autoimmune diseases, such as the neuropsychiatric systemic lupus erythematosus, Hashimoto's thyroiditis and multiple sclerosis are often associated with symptoms of mania and depression (Carta et al., 2014; Rege and Hodgkinson, 2013).

* Correspondence to: Bipolar Disorders Unit, Hospital Clínic, IDIBAPS, CIBERSAM, C/ Villaroel 170, 08036 Barcelona, ES, Spain.
E-mail address: EVIETA@clinic.cat (E. Vieta).

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The association between thyroid alterations and mood disorders has been known for some time (Whybrow et al., 1969). It has been suggested an implication of hypothalamic–pituitary–thyroid (HPT) axis on neuropsychological deficits of BD (Bonnin et al., 2010). High rates of thyroid dysfunction have been found in patients with BD, compared to the general population (Goodwin and Jamison, 2007). Many studies show a possible relationship between circulating thyroid autoAbs, including anti-thyroperoxidase (TPO-Abs), and affective disorders even in the absence of thyroid hormone abnormalities (Leyhe and Mussig, 2014). A higher prevalence of thyroid autoAbs was found among patients with BD, even in the absence of thyroiditis (Kupka and Regeer, 2007). Thus, thyroid alterations may play a role in the pathophysiology of BD, although their exact role, if any, has not been fully elucidated. Pharmacological treatment, especially lithium, which is considered the mainstay of BD treatment, might be also implicated as a predisposing factor for the development of autoimmune thyroiditis (AIT) (Chakrabarti, 2011). Furthermore, it is widely recognized that two important factors, age and sex, may influence the incidence of thyroid autoimmunity: middle-aged women are known to show the highest prevalence rates (Bocchetta and Loviselli, 2006).

In autoimmune thyroid disease, increased levels of autoAbs against thyroperoxidase (TPO-Abs), previously named anti-microsomal (M-Abs), against thyroglobulin (TG-Abs) and against thyroid-stimulating-hormone-receptors (TRAbs) are commonly found (Nielsen et al., 2004). The prevalence of TPO-Abs seems to be higher in autoimmune hypothyroidism and Grave's disease (GD). The positivity for TG-Abs has been found in less than 60% of patients with lymphocytic thyroiditis and 30% of GD (Silva et al., 2003). TRAbs were found to be increased in GD and atrophic thyroiditis (Boelaert and Franklyn, 2005).

The major aims of the present systematic review are to better elucidate the relationship between BD and thyroid autoimmunity and the possible evidence of a primary autoimmune thyroid response in BD patients. Also, we aimed at reviewing the role of lithium treatment and sex in the prevalence of thyroid autoimmunity among BD patients. Finally we will discuss the potential research implications of our findings for future studies.

2. Method

This review has been conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements (Liberati et al., 2009) (see Fig. 1).

2.1. Search strategy and selection of studies

Studies were identified through three methods. First, a comprehensive computerized literature search in three bibliographical databases – MEDLINE, EMBASE and PsycInfo – from inception to January 28th, 2017 was performed. Search strings are provided in the Supplementary material S1 that accompanies the online edition of this article. Second, this search strategy was augmented through tracking citations of included articles in Google Scholar. Finally, we conducted a manual reference check of accepted papers to supplement the above electronic searches (see references of studies excluded after full-text review in the Supplementary material S2). No language restrictions were applied. Two investigators screened title/abstracts for potential eligibility. Disagreements were resolved through consensus. References selected for full-text review were evaluated by two independent raters. Disagreements were resolved by discussion. When there were overlapping samples in different studies, we included the one with the largest dataset. We included observational studies (cross-sectional, case-control and cohort studies) in which data on patients meeting either DSM or ICD criteria for BD and frequency or incidence of autoimmune thyroid pathologies (or frequency of positive thyroid autoAbs or as a continuous measure) were clearly reported. We also included studies investigating the prevalence of autoimmune thyroid pathology or thyroid autoAbs (positivity or continuous measure if compared to controls) in unaffected first-degree relatives or unaffected twins of individuals with BD. Studies were excluded if they: involved less than ten bipolar patients; reported other psychiatric disorders, and did not provide data for BD separately; reported thyroid function assays without autoAbs; reported thyroid pathology but did not specify if these conditions were autoimmune.

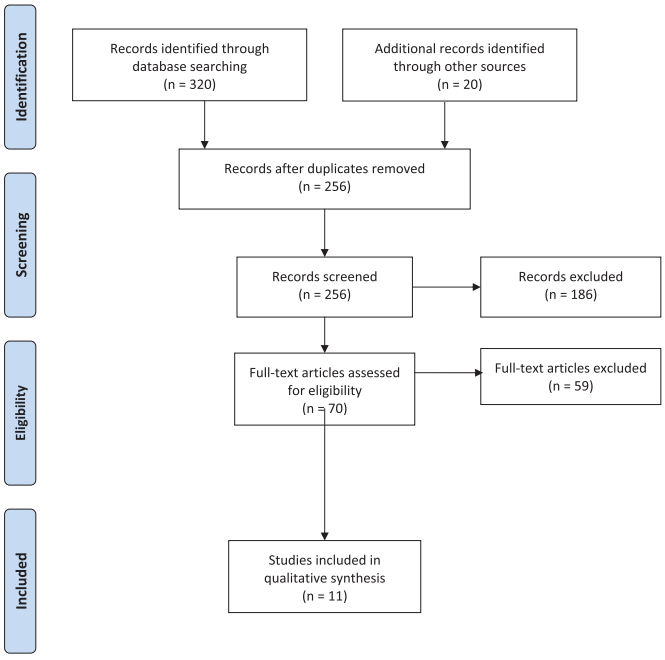

Fig. 1. PRISMA flow diagram of the selected and included studies.

2.2. Data extraction and quality assessment

Using a structured spread sheet, data on the following characteristics were extracted: author, publication year, study design, sample size, autoimmune thyroid pathology and anti-thyroid antibodies. We appraised the quality of included studies by using the Newcastle-Ottawa Quality Assessment Scale (NOS) (Wells et al., 2014) in which a study is judged on three broad perspectives: the selection of the study groups; the comparability of the groups; the ascertainment of either the exposure or outcome of interest. Two authors extracted data and assessed each included study according to the NOS criteria (See Supplementary material, Table 1). Disagreements were resolved through consensus.

2.3. Synthesis of results

Due to the anticipate heterogeneity in terms of study design, participants and outcomes, we conducted a narrative synthesis of the available studies.

3. Results

3.1. Systematic search results

The global search first returned 340 titles, and 256 were available after the removal of duplicates. We selected 70 studies to assess the full-text. Subsequently, we excluded 59 of the retrieved articles (reasons for exclusion are provided in Supplementary material, Table 2). A total of 11 original studies met our inclusion criteria (Barbero et al., 2014; Bartalena et al., 1990; Cobo et al., 2015; Eaton et al., 2010; Haggerty et al., 1990, 1997; Hillegers et al., 2007; Hornig et al., 1999; Kraszewska et al., 2015; Kupka et al., 2002; Vonk et al., 2007).