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Association between Hashimoto's Thyroiditis and Multiple sclerosis: a systematic review of observational studies

Σχέση μεταξύ θυρεοειδίτιδας Hashimoto και Σλήρυνσης κατά Πλάκας: μια συστηματική ανασκόπηση μελετών παρατήρησης

A thesis submitted in fulfillment

of the requirements for the degree of

Master of Science in Medical Research Methodology

By

Stergios Karalis

Larissa, September 2021

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Abbreviations

- HT – Hashimoto Thyroiditis
- AD – Autoimmune disease
- ATD – Autoimmune Thyroid Disorder
- MS – Multiple Sclerosis
- CNS – Central Nervous System
- EBV – Epstein-Barr virus
- VZV – Varicella zoster virus
- CSF – Cerebrospinal fluid
- Tg - thyroglobulin
- TPO – thyroid peroxidase
- TREG – regulatory T cell

Abstract

Background

Hashimoto's thyroditis (HT) is a very common disease of the thyroid gland which is recognized as an autoimmune thyroid disorder (ATD). Multiple Sclerosis (MS) is a well known and frequent autoimmune disease with a high spectrum of clinical demonstration. Scientific interest has focused recently on the possibility of concomitant existence of both diseases and the correlation between them.

Objectives

This study focuses on investigating the association between HS and MS by synthesizing the data of pertinent existing literature.

Search methods

The search strategy included the electronic databases MEDLINE, EMBASE and Cochrane, and grey literature. The search resulted in 5 relevant studies, contained in the systematic review.

Selection criteria

This systematic review synthesizes data from observational studies written in English language. These studies had to report data about developing MS and HT in the ambit of autoimmunity and possible risk factors. There were no race, ethnicity or chronological limits of rejection. Studies that presented subjects with other medical history were excluded.

Data collection and analysis

All studies were inspected, at first by title and abstract, and subsequently by full text. Conflicts concluded through mutual agreement. All studies were evaluated for their quality and bias risk. Data were extracted using a data extraction form formulated in Microsoft Excel spreadsheet.

Results

Five studies were included with a total population of 7,011 subjects. Between the outcomes provided were a high frequency of comorbidity with MS and HT from 0.9% up to 7%. Also, a three-fold increased risk of HT in females with MS is mentioned. Strong evidence observed that HT is the most common autoimmune disorder within families predisposed to autoimmunity (24%) and also within families with a background of autoimmunity. OR having both disorders in individuals were 0.9, (0.2-6), 95% CI and within relatives of MS cases OR=1.92(1.1-3.6), 95%CI. Finally, the increased expression of BACH2 and FOXP3 genes in cases with MS and HT with high levels of significance (p=0.05 and p=0.002), constitutes strong evidence that they play an important role in the pathogenesis and possibly the coexistence of these diseases.

Conclusions

This study provided evidence that Hashimoto's thyroiditis and multiple sclerosis have an increased rate of appearance in coexistence. Screening for and relieving the shared pathogenetic paths and risk factors of the two autoimmune diseases could improve the prevalence and the prognosis of them.

Keywords: multiple sclerosis, Hashimoto's thyroiditis, coexistent autoimmune diseases, polyautoimmunity, gene expression

Περίληψη

Υπόβαθρο

Η θυρεοειδίτιδα Hashimoto είναι μια πολύ συχνή νόσος του θυρεοειδούς αδένα που χαρακτηρίζεται από καταστροφή του θυρεοειδούς αυτοάνοσης αιτιολογίας. Η σκλήρυνση κατά πλάκας είναι ένα ευρέως γνωστό και συχνό αυτοάνοσο νόσημα με ευρύ φάσμα κλινικών εκδηλώσεων. Το επιστημονικό ενδιαφέρον πρόσφατα έχει εστιάσει στην πιθανή ταυτόχρονη συνύπαρξη και των δύο νοσημάτων και τη μεταξύ τους συσχέτιση.

Στόχοι

Η συγκεκριμένη μελέτη εστιάζει στη διερεύνηση της σχέσης μεταξύ της θυρεοειδίτιδας Hashimoto και της σκλήρυνσης κατά πλάκας συνθέτοντας δεδομένα από συναφή υπάρχουσα βιβλιογραφία.

Ερευνητικές μέθοδοι

Η ερευνητική στρατηγική συμπεριέλαβε τις βάσεις δεδομένων MEDLINE, EMBASE και Cohrane καθώς και εκδόσεις περιορισμένης κυκλοφορίας. Η έρευνα κατέληξε σε πέντε σχετικές μελέτες που συμπεριλήφθηκαν στη συστηματική ανασκόπηση.

Κριτήρια επιλογής

Η συγκεκριμένη συστηματική ανασκόπηση συνθέτει δεδομένα από μελέτες παρατήρησης δημοσιευμένες στην Αγγλική γλώσσα. Οι μελέτες αυτές έπρεπε να αναφέρουν δεδομένα που αφορούν την εκδήλωση σκλήρυνσης κατά πλάκας και θυρεοειδίτιδας Hashimoto στο πλαίσιο αυτοάνοσης διεργασίας καθώς τους πιθανούς παράγοντες κινδύνου. Δεν υπήρχαν περιορισμοί αποκλεισμού που να αφορούν την φυλή, την εθνότητα ή τη χρονικότητα. Οι έρευνες που αφορούσαν περιπτώσεις με άλλες συνυπάρχουσες παθήσεις αποκλείστηκαν.

Συλλογή δεδομένων και ανάλυση

Όλες οι μελέτες εξετάστηκαν από δύο ανεξάρτητους κριτές, αρχικά σύμφωνα με τον τίτλο και την περίληψη και έπειτα με το πλήρες κείμενο. Οι ασυμφωνίες απόψεων επιλύθηκαν με κοινή συναίνεση. Όλες οι μελέτες εκτιμήθηκαν για την ποιότητα και τον κίνδυνο αμεροληψίας τους. Τα δεδομένα αποσπάστηκαν με τη βοήθεια ειδικής φόρμας σε Microsoft Excel.

Αποτελέσματα

Πέντε μελέτες συμπεριλήφθηκαν με συνολικό αριθμό 7,011 ατόμων μελετήθηκαν. Μεταξύ των αποτελεσμάτων που προέκυψαν ήταν η μεγάλη συχνότητα συνύπαρξης της σκλήρυνσης κατά πλάκας με την θυρεοειδίτιδα Hashimoto που κυμαίνεται από 0.9 εώς 7%. Επίσης, αναφέρθηκε τριπλάσιος κίνδυνος εμφάνισης θυρεοειδίτιδας Hashimoto σε γυναίκες που πάσχουν από σκλήρυνση. Παρατηρήθηκε ισχυρή ένδειξη ότι η θυρεοειδίτιδα Hashimoto είναι η πιο συχνή αυτοάνοση νόσος σε οικογένειες με οικογενή προδιάθεση για αυτοανοσία με συχνότητα 24% αλλά και η πιο συχνή συνυπάρχουσα σε άτομα με σκλήρυνση κατά πλάκας. Παρατηρήθηκε λόγος πιθανοτήτων για συνύπαρξης και των δυο νόσων σε μεμονωμένα άτομα 0.9(0.2-6), 95% CI και μεταξύ συγγενών ατόμων που πάσχουν από σκλήρυνση κατά πλάκας OR=1.92(1.1-3.6), 95% CI. Τέλος, η αυξημένη έκφραση των γονιδίων BACH2 και FOXP3 σε περιπτώσεις ατόμων με hashimoto και σκλήρυνση στατιστικά σημαντική (p=0.005 και p=0.002), αποτελεί ισχυρή ένδειξη ότι αυτά παίζουν σημαντικό ρόλο στην παθογένεση και πιθανόν και στη συνύπαρξη αυτών των νόσων.

Συμπέρασμα

Η συγκεκριμένη μελέτη παρέχει αποδείξεις πως η θυρεοειδίτιδα Hashimoto και η σκλήρυνση κατά πλάκας εμφανίζουν αυξημένη πιθανότητα ταυτόχρονης εμφάνισης. Ο έλεγχος και ο εντοπισμός των κοινών παθογενετικών μηχανισμών και των παραγόντων κινδύνου των δύο αυτοάνοσων νοσημάτων θα μπορούσε να βελτιώσει τον επιπολασμό και την πρόγνωσή τους.

Λέξεις κλειδιά: σκλήρυνση κατά πλάκας, θυρεοειδίτιδα Hashimoto, συνυπάρχοντα αυτοάνοσα νοσήματα, πολυαυτοανοσία, γονιδιακή έκφραση

Background

Multiple sclerosis is the most common autommune disease which affiliates with demyelination of the central nervous system (CNS). MS is identified by sections of demyelination oligodendrocytes loss and astrogliar scarification(1). Axonal damage is noticeable in later phases. MS has a high variety of progress and many atypical forms(2,3).

Clinical suspicion of MS is a multifactorial task. It mostly affects adults of a young age who exhibit one or more episodes of central nervous system malfunction developed from hours to days with at least partial lysis after a period of weeks to months. Clinical symptoms may be monofocal (when one area of CNS injury is observed) or multifocal (consistent with more than one areas)(2,3).

The diagnostic course includes clinical symptoms of MS, characteristic magnetic resonance imaging (MRI) findings with variant advance and cerebrospinal fluid analysis. McDonald criteria synthesizes these findings to the diagnose(4,5).

Epidemiologically, MS is a disease diagnosed mainly in young adults that has more impact in women than men with an estimated ratio of 1.4:1 to 2.3:1(6). This ratio seems to increase according to recent studies(7,8). It is believed that the mean age of appearance is between 28 to 31 years of age but many cases may differ a lot on the onset of the disease's manifestations, from the early first years to the seventh decade of life. However it depends on the type of MS(9). Many observational studies conclude that patients with MS are more likely to have other diseases of autoimmunity. In a meta-analysis study, autoimmune thyroid disease and psoriasis seem to most likely are acompanied with MS(10). In addition, other studies have described the increased rate of developing MS in the existence of other autoimmune diseases(11). Many different studies have described over 200 polymorphisms related to MS, among the strongest of all are certain genes of the major histocompatibility complex (MHC), especially HLA-DRB1. Non-MHC genes also effect to the probability of suffer from MS like CD6, CLEC16A, IL2RA, IL7R and polymorphisms of it, IRF8 and TNFRSF1A(12-15). Also, a study of 466 Australian MS patients and 498 controls expressed that vitamine D response element (VDRE) wich is located in HLA-DRB1 gene possibly interacts with the gene

itself to raise the risk of MS with odds ratios ranging from 0.28 to 3.06(16). Another study in Sardinia where MS has high prevalence concluded that not only VDRE and HLA-DRB1 (and mutations of it) presence but also polymorphisms in B-cell activating factor (BAFF) relates to the presence of MS(17).

MS is considered a heterogenous disease with a vast variety of clinical symptoms and radiological imaging that reflect diverse paths to tissue injury. There are three primary mechanisms that cause MS: inflamation, demyelination and the degeneration of the axon. Nevertheless the cause is little known. The main theory of great acceptance is that MS as an inflamation process caused by lymphocytes. As the disorder progress, microglia engages and neuronical degeneration appears(5,30).

Familial MS percentage differ in multiple studies described from 3 percent to 23 percent. In a Danish population study of 8205 cases with MS the relative risk of MS was up to seven times higher (95% CI 5.8-8.8) in first degree relatives(18).

It is also known that the prevalence of MS is associated with the sex of the affected parent. Even though the results of many studies differ from one another, it is believed that epigenetic mechanisms in DNA linking during cell division, drive to straight transmition from the affected parent(19-21).

There is a certain relation to enviromental factors and the risk of MS. Although there are not clear confirmations, viral infections have been associated with MS(22). Several studies including a meta-analysis of 14 case control and cohort studies suggest association between Epstein-Barr virus (EBV) and increased risk of MS possibly due to existence of EBV on the cerebral tissue(23). Varicella zoster virus (VZV) has also been linked to progressive type of MS in some studies due to presence of viral particles and DNA in cerebrospinal fluid (CSF) of patients. In contrast, other studies occur that cytomegalovirus infection in pediatric patients has protective role(24).

Vaccination as a trigger of the immune system have not been associated with MS despite multiple examinations of this hypothesis(25,26).

Geographic factors seem to affect the prevalence of MS(27). Europe, southern Canada, northen United States, New Zealand and southeast Australia have the highest frequency of the disease from 60 to 300 cases per 100.000. These differences perhaps could be explained by racial distinction. White populations have observed to have the highest prevalence(28).

Many studies have described the inverse connection between sun exposure and vitamin D serum levels and MS frequency. Based upon studies these factors it has a protective role in the development and progression of the disease(29).

Hashimoto's disease also known as chronic autoimmune (lymphocytic) thyroiditis, acounts for the most common cause of thyroid underfunction in iodine sufficient areas globally. Mostly autoimmune incidents lead the thyroid gland to destruction and underfunction. The majority of patience have high serum concentrations of antibodies against one or multiple antigens of the thyroid gland. Lymphocytic infiltration of the thyroid primarily B and T cells provoke gradual thyroid failure. There are two basic types of clinically distinction of HT, goitrous autoimmune thyroiditis and atrophic autoimmune thyroiditis (also recognised as primary myxedema). HT mostly affects women with a sex ratio of 7:1 and concerns pediatric patients also(31).

Even though thyroid enlargement is usually asymptomatic, some patients have neck pain or tenderness resulting from intensive or rapid swelling. These patients seek surgical relief. Other mild forms of the disease are postpartum thyroiditis and silent thyroiditis wich may be subclinical conditions but gradually evolve to thyroid failure. The common path of HT is step by step thyroid failure. Hypothyroidism when overt is permanent in almost all patients. This is exhibited at a rate of 5 percent annually(32).

Lymphocytic infiltration is the main histopathological find that cause either decimation of thyroid follicle cells to become fibrosis areas or hyperplasia as a result of thyroid stimulating hormone (TSH) response. In the course of the autoimmune process B cells are triggered to produce thyroid antibodies to thyroglobulin (Tg) and antibodies to thyroid peroxidase (TPO)(33). These polyclonal antibodies are more often immunoglobulin IgG1 and IgG3. Antibodies to the Thyroid stimulating hormone (TSH) also found in HT patients' serum. These are also polyclonal antibodies who act as TSH receptor blockers and tend to obstruct

the production of thyroid hormones. TSH receptor stimulating antibodies may also be found, incompetent to trigger the damaged thyroid gland. All these antibodies can cross the placenta and affect thyroid activity. In their part, T cells respond to thyroid antigens and produce cytokins who lead to the production of a variety of immune cells. Overall, T cells action consists advancing the production of antibodies, production o cytotoxic T cells and destruction of thyroid follicle cells and maintaining homeostasis via regulatory T cells (TREGs). Patients with HT seem to lack of immune regulation as a result of depleted numbers or low potency of regulatory suppression cells such as CD4+, CD25+ and Foxp3+(34).

Controversy exists in screening and diagnosing autoimmune diseases. The purpose of screening is to find patients with HT or MS and predict the probability to develop the other. Scientific researchers find difficulties to this purpose due to lack of evidence in the preclinical stages of autoimmune diseases.

Objectives

The aim of this systematic review was to search the literature to accumulate, analyze and synthesize data in the quest of finding an association between Hashimoto thyroiditis and multiple sclerosis. If proven, this correlation would be of clinical interest as it would propose accordingly screening and timely diagnose and treating of patients suffer from MS or HT due to higher risk of developing the other.

Methods

Inclusion and exclusion criteria

Population

This systematic review included prospective observational studies with a target population of cases with the foresaid autoimmune diseases(35-39). These patients had to be on no medication other than those routinely administered for the symptoms and therapeutic approach of these diseases. Population from any ethnicity was included. Studies which investigated cases with a medical history of any other chronic conditions before the study

were excluded. Studies involving only a subset of relevant participants were managed by subgroup analysis. When this course of action was not possible due to lack of data, the studies were excluded.

Exposure

The exposure was deemed to be genetic and familial factors associated with MS and HT. There was no temporal restriction in the onset of the diseases, nor the classification to cite which ones where present in each case. All study cases had to be diagnosed with MS and HT by a physician according to their clinical symptoms, serum examinations and radiological imaging.

Comparator

The prevalence of patients with coexistant MS and HT was compared with the prevalence of patients with only one of the two autoimmune diseases.

Outcomes

The greatest outcome of this study was to demonstrate the shared risk of MS and HT.

Study design

This systematic review included prospective observational studies of cases with autoimmune diseases (MS and HT). Based on the result of this review these studies classified in three subgroups, patients with HT, patients with MS and patients with MS+HT.

Search strategy

To conduct this review, a search strategy was formulated to obtain the eligible studies. The first step of this procedure was a search of three online medical databases, the MEDLINE (through Pubmed search engine), the EMBASE (through Scopus search engine) and Cochrane Library Database (from their official webpage).

Grey literature, conference abstracts of major international conferences and medical meeting summaries were searched online to ensure no important studies are left out of the review.

The search strategy included a combination of free text and Medical Subject Heading (MeSH) terms, including synonyms and relevant terms. In more detail:

Pubmed search string

(("Hashimoto Disease"[Mesh] OR "Hashimoto Struma"[tw] OR "Hashimoto Thyroiditis"[tw] OR "Thyroiditis Hashimoto"[tw] OR "Hashimoto's Syndrome"[tw] OR "Chronic Lymphocytic Thyroiditis"[tw] OR "Chronic Lymphocytic Thyroiditis"[tw] OR "Chronic Lymphocytic Thyroiditis"[tw]) AND ("Multiple Sclerosis"[Mesh] OR "Sclerosis"[tw] OR "Disseminated Sclerosis"[tw] OR "MS"[tw] OR "Multiple Sclerosis"[tw] OR "Acute Fulminating"[tw]))

The Pubmed database search resulted in 124 articles.

Scopus search string

TITLE-ABS-KEY (("Hashimoto Struma" OR "Hashimoto Thyroiditis" OR "Thyroiditis Hashimoto" OR "Hashimoto's Syndrome" OR "Chronic Lymphocytic Thyroiditis" OR "Chronic Lymphocytic Thyroiditis" OR "Chronic Lymphocytic Thyroiditis") AND (Sclerosis OR "Disseminated Sclerosis" OR "MS" OR "Multiple Sclerosis" OR "Acute Fulminating"))

The Scopus database search resulted in 337 studies.

Cochrane search string

("stress" OR "stress*" OR "psychological stress" OR "psycholog*" OR "mental" OR "emotional" OR "psychosomatic" OR "conceptual" OR "cognitive" OR "subjective" OR "subliminal") AND ("gestational diabetes mellitus" OR "GDM" OR "gestational diabetes" OR "pregnancy diabetes") (Word variations have been searched)

The Cochrane database search resulted in 0 studies.

All studies resulted from the above search strategy were evaluated and screened independently. The primary search located 461 articles. Identical studies were removed.

Based on title and abstract text, 32 articles remained. Following rejection based on full-text content 5 articles remained that audit the relation between multiple sclerosis and Hashimoto thyroiditis. Because of the existence of missing values, the reviewers endeavored to contact the authors in order to obtain useful data for the analysis; However, neither replied to the e-mails. The flow chart of the search strategy is presented in Figure 1.

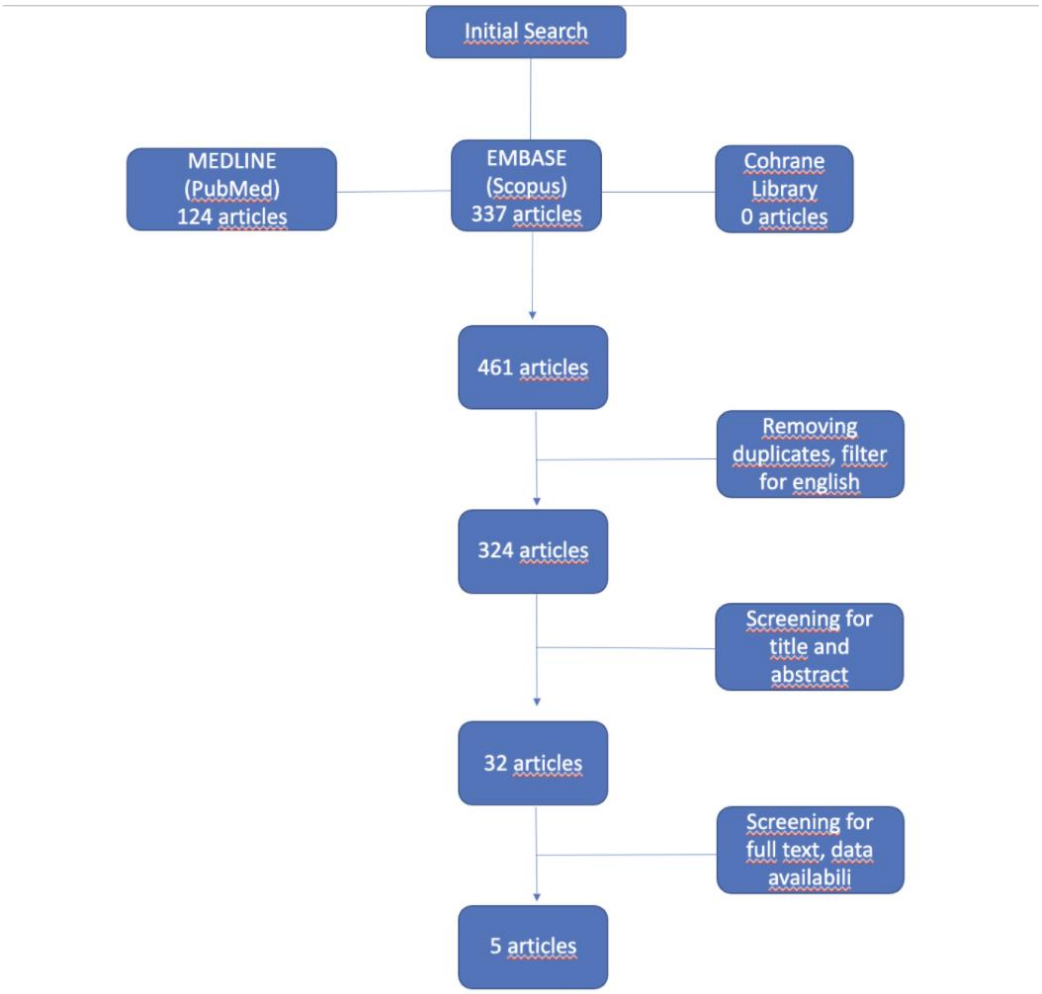

Figure 1. Search strategy

Data extraction

Data collection process

Data was gathered from the studies contained in this review. Data given from the studies were inserted into forms that were designed using Microsoft Excel software.

Extracted variables

According to the collected data forms the informations of interest was assembled. The inconsistencies and irregularities found were managed after agreement.

The information gathered from the studies included:

• Study information (authors, year of publishing, journal of publishing, digital object identifier (DOI) number, type of study, type of analysis, size of sample)

• Participant's characteristic variables (age, sex, existing autoimmunity, familial inclination)

• Exposure characteristics (genetic factors and blood relation)

• Primary outcome (number of cases with coexistance of MS and HT)

Risk of bias assessment

Every study included was assesed in order to verify the risk of bias. The areas of bias examined were:

• Selection bias

• Information bias

• Reporting bias

• Cofounding bias

The reviewers had to determine the score of each bias category based on the content of the studies. In the selection bias category, they inspected the sample of participants, their characteristics and the measures concidered for their selection. They were associated with the disease or judged based on other external factors. If the time interval was satisfying and if the exposed and unexposed group were similar apart from the exposure. In the information bias category, the reviewers had to decide whether the acquired information of the outcome has been extracted in identical way in both of the participant's groups. Reporting bias was evaluated by checking if all the data were documented, dissregarding the outcome. Last of all, confounding bias was assessed in order to detect the presence of factors related to the exposure and the outcome that have not been evaluated and may have an effect to the results. In every single of the detailed sections, ach study was properly rated as of “high risk”, “low risk” or “unclear risk”.

The “Risk of bias summary” (Figure 2) summarizes the evaluation of the reviewers about the risk of bias for each included study. The “Risk of bias graph” (Figure 3) illustrates the risk of bias of each category as percentages in all studies included.

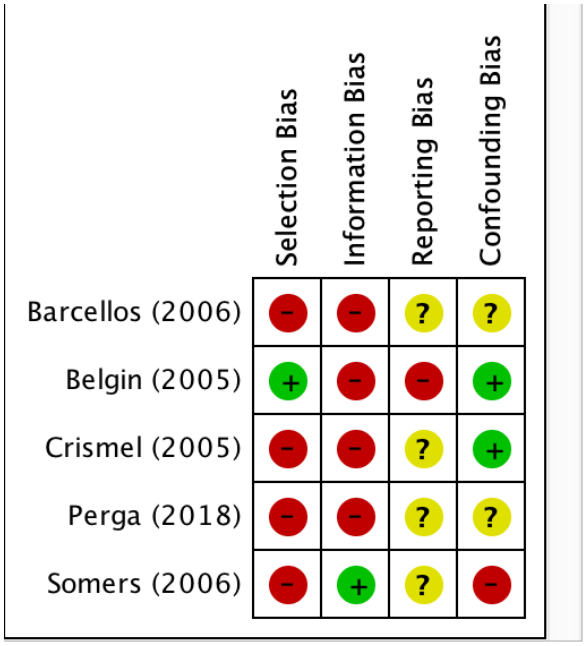

Figure 2.Risk of bias summary

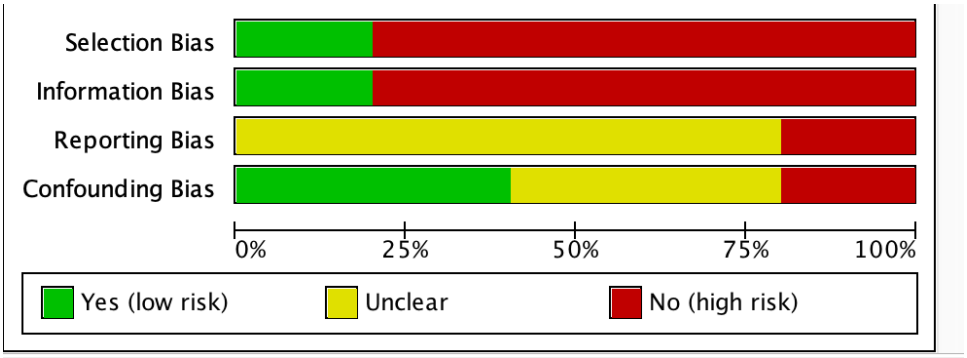

Figure 3.Risk of bias graph

Explanation of the rating of each study bias will adhere to alphabetical order. In Barcellos et al.(38) study, the population studied was randomly selected with an index case of MS in each family. None of the cases were exluded so there is a small selection bias risk. In the course of the reseach, only index cases were contacted through a questionaire followed by a phone call if not replied. Index cases also provided the information needed about family members.They compiled if there was an incident of autoimmune disorder in the family and were asked to mention the symptoms and if there was an official diagnose. If not the cases were characterized as negative for a disease in order to avoid information bias. There are no evidence for confounding bias in this report.

The study of Belgin et al.(36) was rated with an icreased confounding bias risk. There is no evidence of subjects previous medical history or family history of autoimmunity. Also a high selection bias was detected due to the small sample of participants.

The study of Criswell et al.(35) included families that required to have at least two members affected by the autoimmune diseases studied. The selection bias characterized small because it took place through random patient advocay groups, publications (e.g., the American Autoimmune Related Diseases Association[AARDA], Multiple Sclerosis Quarterly Report etc) and directcommunication with physicians' offices. Demographic and clinical information collected via telephone or mailed questionaire. Subjects who described at least one condition were asked for additional clinical information (date of diagnosis and information of the doctor, symptoms and treatment received). This way the researchers attenuated the information bias. Confounding bias was high due to race (white race studied) which is known as strongly associated factor of autoimmunity and coexistence of multiple

autoimmune diseases studied and the unknown correlation betwean them. Reporting bias was high due to lack of information about other conditions and characteristics of the subjects (past medical history).

The Perga et al.(39) Study includes pre-screened groups of population objectively represented. The criteria of inclusion suggested no signs of acute infection for a past time of thirty days and the lack of coexisting medical conditions. Sample collection and processing was done based on strict protocol approved by the local Ethics Comitee of University Hospital San Luigi Gonzaga, Piedmont region.

The Study of Somers et al.(37) was rated as high information bias because of the absence of presentation of all the outcomes in the review. The uncontrolled studies were excluded from the results in order to constrain confounding bias. Vast heterogeneity of population is mentioned. Although the publication bias is unclear.

Results

This systematic review included 5 studies, with the common characteristic of having as a main or secondary objective the presentation of augmented prevalence of MS and HT coexistence. A review of the results of each study follows, put in chronological order.

Belgin et al.(36) presented two cases of patients with definite MS, that satisfy the criteria of HT. These patients were selected through a group of 106 (62 women and 44 men) MS definite patients. The prevalence of coexistence was 1.89%. They described common symptoms of both like muscle weakness, fatigue and myalgia and suggested the need of thyroid function testing when they occur in MS patients. They also refered to the 3-fold increased risk of HT in female patients with MS and the importance of thyroid screening of patients with MS when treated with interferon-β or Campath-1H.

Criswell et al.(35) investigated eight autoimmune diseases of high prevalence to prove evidence for genetic tendency. On this basis, researchers studied 265 families affected with the autoimmune diseases studied (constituted by 806 affected individuals and 97 affected with two or more diseases) with an average of 3.2 affected per family. Statistical measures

were used to compute the connection of specific autoimmune diseases and the appearence of of PTPN22 allele. Study indicates that Hashimoto thyroiditis was the most common throughout all affected subjects followed by multiple sclerosis. Also the prevalence of MS and HT coexistence among subject was 1.4%(13 out of 907 cases). In a deal of effort to affiliate these results with the PTPN22 R620W allele, no significant association with MS but important connection with HT (OR 1.63%, 95% CI 1.24-2.17) in a total of 746 affected members of these families in comparison with 2,064 control subjects. The large sample of MS patients (120 participants) and the lack of association with PTPN22 knowing that is required for T-cell receptors (TCR) to adjoin, may suggest multiple pathogenetic mechanisms for the disease.

Sommers et al.(37) examined in a systematic review proof of the coexistence level within 4 TH1-associated diseases of subjects. Familial connection of autoimmunity concerned this study which included 54 of the 1187 screened articles published until March 2004. In 5 studies of individuals from a total number of 2,288 MS cases found 20 cases of MS with comorbid HT (0.9% prevalence of coexistence). From these, Broadley et al. (2000), a case control study with 571 MS cases and 375 controls, refers to an OR=0.9 (0.2-6) 95% CI. Also, among relatives it describes an OR=1.92 (1.1-3.6) 95% CI.

Barcellos et al.(38) studied a population of 176 families with at least one index case of MS (176 index cases of MS and 1317 first degree relatives including 210 with MS in a total of 1493 cases) in order to observe the incidents of coexistence MS with 31 other immune mediated disorders. 10% of index cases and 7% overall reported diagnosed HT. HT was the most commonly present disease in families with at least one MS case (24%). In conclusion, for index cases of MS with coexisted diagnosis for HT, the odds for these diseases to appear in family members were up to 4.8 times augmented with an OR=4.8, 95% CI 1.7-13.5.

Finally, Perga et al.(39) had a main goal of breaking shared molecular paths of MS and HT through examining common genetic risk factors. The study analyzed and examined the expression of certain genes (TNFAIP3, NR4A family, BACH2, PDCD5 and FOXP3), TREG levels and 25-OH Vitamin D serum levels. TNFAIP3 and NR4A family are effective inhibitors of NF-kb path. Malfunctions of their expression are linked to numerous autoimmune disorders including MS. A notable degreased expression of both genes observed in MS+HT patients

compared with HC and HT group but did not reach high level of significance. Similar deregulation but statistically significant inspected in MS group compared with HC and HT (p=0.04 and p=0.05 for TNFAIP3 and p=0.03 and p=0.002 for NR4A family) showing a specific MS-pathogenetic mechanism . BACH2, PDCD5 and FOXP3 are also NF-kb target genes, specifically BACH2 and FOXP3 are TREG transcription factors. BACH2 showed high levels of expression in all three groups HT, MS and MS+HT in comparison with the control group (p=0.01, p=0.0006 and p=0.005). Comparable results were shown in FOXP3 analysis (p=0.01, p=0.04 and p=0.002). PDCD5 gene expression was higher in the three groups but MS+HT group did not reach a level of significance. Statistical significance TREG and 25-OH vitamin D levels also didn't reach. Potent pathogenetic factors of both disorders were BACH2 and FOXP3 accordind to the results wich were overexpressed with the MS+HT group at the highest level.

Discussion

Hashimoto's thyroiditis is the most frequent cause of thyroid malfunction in the iodine-sufficient populations and the dominant autoimmune thyroiditis(31). Its prevalence is up to 1.2% of world population in different studies and increases with age and has concerns mostly females with a ratio 7:1. It may appear in a varied forms and cause thyroid disfunction and gradually failure(32). There are many allegations for the pathogenetic mechanisms of the disorder but it is well known that is a combination of genetic tendency and environmental factors. The presence of auto-antibodies leading to self destruction of thyroid gland is the base of its autoimmune nature(34).

Multiple sclerosis is the most common cause of demyelination of the central nervous system. It is heterogenous with different clinical forms that all lead to inflamation, demyelination and axon degenaration that may lead to inveteracy(1). It affects mostly the female population with a ratio up to 2.3:1, at a mean age of onset 30y.o. and diverse prevalence observed in differend geographical regions(2). Although its pathogenesis is yet unknown there are many theories refering to possible mechanisms of appearence, all of them strictly associated with autoimmune background(6). Also there are many factors that

alter the number of MS cases (such as genetic, geographic, environmental)(18-29). Despite the fact that there are plenty of methods contributing to MS diagnosis (imaging, cerebrospinal fluid analysis, serum testing for auto-antibodies and optical coherence tomography), the evaluation of suspected cases is often clinical.

Concidering the gravity and high presence ratio of these disorders it would be significant for public health to evaluate and expose the mechanisms that they occur as long as the risk factors that are involved to their presentation. Some risk factors are inevitable such as familial occurence of autoimmunity, genetic inclination and age of presentation but there are others that can be avoided including late treatment, late diagnosis, some environmental factors and lifestyle. The fact that there are multiple evidence that the presence of an autoimmune disorder predispose to polyautoimmunity is of great importance in order to ameliorate the clinical condition of cases.

Some limitations restrain this systematic review. First of all the studies included were relatively low in number. This is anticipated due to frugal amount of articles published of the sample population but could affect the results that extracted from the review. The fact that none of the studies encompassed was fully unbiased was already cited. This may affect the quality and validity of the conclusion of this review. An additional restriction of the current study is that articles that were reviewed researched the coexistence of the two disorders from different aspects (familial and genetic factors). Even though every study had as main interest the simultaneous occurrence of the two, statistical data was limited in order to extract a total outcome.

Finally, coexistent MS and HT is a case diagnosed when using the appropriate screening laboratory, imaging and clinical investigations to the appropriate population and at the right time in the course of autoimmunity. According to the evidence ther are specific genetical expressions that leads to the well observed event of the simultaneous presence of the two. Nevertheless, several autoimmunity risk factors that are still unknown and how they interact may be a confounding agent in the effort of understanding autoimmunity. Thus, further studies searching these mechanisms are vital.

Conclusions

This systematic review attempted to gather all studies that had the main purpose to investigate the relation between Hashimoto Thyroiditis and Multiple Sclerosis. In the course of this review many indications were shown that imply a common prevalence of the two diseases possibly due to shared pathogenetical pathways. The high prevalence of coexistence as long as the proof of genetic risk factors expressed at a higher level in these cases imply there is a strong association between them. Even though they differ as clinical entities, their autoimmune nature seems to relate to their simultaneous existence. Although the number of studies that have been included in this review was significantly low and merely biases, they deepened the already known clinical suspicion. The research regarding the connection of them could clarify the shared risk of autoimmunity and provide a model of prompt screening, diagnosis and treatment to people with augmented chance of autoimmune disorders. In addition, neurologists, endocrinologists and rheumatologists should collaborate with biologists and geneticists to appropriately follow the course of autoimmunity and provide a proportionate treatment to patients.

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