No difference between Hashimoto's thyroiditis and Graves' disease in the association of other autoimmune conditions - systematic review and meta-analysis

Gréta Pham-Dobor[1,2], Lilla Hanák[3], Péter Hegyi[1,3], Katalin Márta[3], Andrea Párniczky[3,4], Marin Gergics[1,2], Patrícia Sarlós[1], Bálint Erőss[1,3], Emese Mezősi[1,2*]

[1]First Department of Medicine, Medical School, University of Pécs, Hungary

[2]Szentágothai Research Centre, University of Pécs, Hungary

[3]Institute for Translational Medicine, Medical School, University of Pécs, Hungary

[4]Heim Pál National Institute of Pediatrics, Budapest, Hungary

*Corresponding author:

Emese Mezősi, 13 Ifjúság, Pécs, Hungary, H-7624, email: mezosi.emese@pte.hu

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Abbreviations: AD- Addison's disease; AITD- autoimmune thyroid disorder; aTg- thyroglobulin antibody; aTPO- thyroid peroxidase antibody; APS- autoimmune polyglandular syndrome; CI- confidence interval; CTLA-4- cytotoxic T-lymphocyte antigen-4; FCRL3- Fc receptor-like protein 3 gene; GD- Graves' disease; HLA- human leukocyte antigen; HT- Hashimoto's thyroiditis; MS- multiple sclerosis; POF- premature ovarian syndrome; PTPN-22- protein tyrosine phosphatase, non-receptor type 22 gene; RA- rheumatoid arthritis; SLE- systemic lupus erythematosus, TSHR- thyroid stimulating hormone receptor antibodies T1DM- type I diabetes mellitus

Abstract

Objective: In autoimmune polyglandular syndromes (APS) both types of Autoimmune Thyroid Disorders (AITDs), i.e. Hashimoto's thyroiditis (HT) and Graves' disease (GD) can be present.

Design: In this meta-analysis, we aimed to provide the first comprehensive overview of the differences between HT and GD in APS II and III.

Methods: Using the MEDLINE and Embase databases all studies containing the keywords of APS II and APS III were screened. Out of 479 studies 18 records containing a total of 1312 patients fulfilled the criteria of our study and were selected for analysis. Meta-analysis was performed using the random-effects model. Results of each meta-analysis were displayed graphically using forest plots.

Results: AITDs were detected in 87.8% of APS patients. HT and GD were specified in 279 and 151 cases, respectively. In the remaining 309 cases, the diagnosis was AITD, without any further characterization. The prevalence of HT, GD and AITD did not differ among APS patients. The pattern of co-associated endocrine, non-endocrine organ-specific and systemic autoimmune disorders was similar in HT and GD. T1DM and AD were found in larger proportion of patients, 70.7% and 18.5%, respectively. Other autoimmune conditions occurred in $\leq$4%. The majority of autoimmunities occurred in dual combinations (91.8%). The combination of four and more autoimmune disorders was published only in HT, in 0.1% of patients.

Conclusions: Using a meta-analysis, no difference could be observed in the prevalence of HT and GD among APS patients and no distinct pattern of co-associated autoimmunities could be established.

Introduction

Autoimmune polyglandular syndromes (APS) are complex, heterogeneous disorders with the combination of autoimmune endocrinopathies and other organ-specific and systemic autoimmune disorders [1-4]. Antibodies against the endocrine and non-endocrine organs can be present [2, 5, 6]. Autoimmune thyroid disorders (AITDs) may occur in APS II and III. APS II is defined by the presence of Addison's disease (AD) and autoimmune thyroid diseases and/or diabetes mellitus (T1DM) [1]. APS III patients have AITDs and any other autoimmune conditions except AD [1-4]. The key regulating genes are common in APS II and III, the HLA, CTLA-4 and PTPN-22 genes [7].

AITDs are multifactorial diseases due to the combination of endogenous, environmental factors and genetic predisposition. There is a strong female predisposition among AITD patients, with a female:male ratio ranging from 5:1 to 10:1 [8].

Hashimoto's thyroiditis (HT) and Graves' disease (GD) are the autoimmune disorders of the thyroid gland, however the two disorders differ in many regards. HT commonly presents with hypothyroidism, whereas GD is a hyperthyroid condition [9]. Th1 pattern of autoimmune reaction is characteristic for HT, whereas the predominance of Th2 cytokines indicates a humoral pattern of immune reaction in GD. However, AITDs encompasses a spectrum of conditions ranging from HT at one end to GD at the other end [9].

A predominance of Th1-mediated immunity in HT may lead to the activation of apoptotic pathways resulting in thyroid cell destruction [10]. The thyroid gland is gradually destroyed leading to reduced thyroid hormone production. HT, also known as chronic lymphocytic thyroiditis is the most common autoimmune disease and is the most common cause of primary hypothyroidism in iodine-sufficient areas [11]. The presence of

autoantibodies against thyroglobulin (aTg) and thyroid peroxidase (aTPO) is the basic humoral immunological feature of HT [12]. HT affects more than 15 % of females and 2 % of males over 60 years [13].

Conversely, the predominance of Th2-mediated immune activity in GD results in the release of thyroid stimulating hormone receptor (TSHR) antibodies, causing thyroid cell hypertrophy and over-activity [10]. GD is typically characterized by a diffuse hyperfunctional goiter. The presence of TSHR antibodies is the most important laboratory feature in the differential diagnosis of GD and HT [12, 13].

Our hypothesis was that due to the Th1 or Th2 predominance of HT and GD, respectively, the prevalence and type of associated autoimmune disorders might differ, however this question has not been investigated previously. Here, we present a systematic review of literature and the first meta-analysis that includes retrospective and cohort studies to verify the differences between HT and GD in APS II and III.

Methods

The study was performed in accordance with the recommendations of the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) statement [14]. The registration number of the work in the international prospective register of systematic reviews is CRD42019126826.

Search strategy

MEDLINE and EMBASE electronic databases were searched using Human filter. No language restriction was applied. The search was completed by 5th November 2018 with the following keywords: "autoimmune polyglandular syndrome", "autoimmune polyendocrinopathies", "autoimmune polyglandular syndrome type II" and "autoimmune polyglandular syndrome type III". Management of references and removal of duplicates was performed by the EndNote software (version: X 7.0.2., Clarivate Analytics, Philadelphia, PA, USA).

Inclusion and Exclusion criteria

The following publications were included: (1) studies reporting cases with two or more autoimmune disorders of endocrine and non-endocrine organs, (2) studies demonstrating data of at least 10 patients. Publications were excluded if (1) a previous study was duplicated, (2) the study focused on patients only with systemic autoimmune disorders. Review articles were also excluded. The records were independently screened by two investigators.

Data extraction

The following information was extracted and populated into an Excel 2016 sheet (Office 365, Microsoft, Redmond, WA, USA) year of publication, type of study, number of

patients included and diagnosed with APS, average age of the patients, sex, main disorders and the combinations of these diseases.

Statistical analysis

For synthesis of data, the methods recommended by the Cochrane Collaboration [15] were applied. Event rates (in percentage distribution) were calculated for dichotomous outcomes. Random effect model was used for all analysis with DerSimonian-Laird estimation [16]. Statistical heterogeneity was analysed using the I^2 and the χ^2 test to gain probability-values; $p<0.1$ was defined to indicate significant heterogeneity. For statistical analyses Stata 15 (Stata Corporation, College Station, TX, USA) was used.

Assessment of the quality of the included studies

The quality assessment of the study was performed by two independent investigators as recommended by Murad et al. in 2018 [17] (Supplementary table 1.). Disagreements between the authors were resolved by discussion, with the involvement of a third review author if it was necessary.

Results

Characteristics of the included studies

After the comprehensive searches of MEDLINE and Embase databases, 479 studies were found. After removing duplicates, we reviewed the remaining 454 studies for the eligibility criteria and identified 118 suitable papers for inclusion in our meta-analysis. Excluding case-reports, 18 articles containing a total of 1312 (10-254/papers) patients were selected for further analysis. Our PRISMA flow chart of the selection process is shown in Fig. 1. Caucasian, Asian and Hispanic ethnicities were included. Characteristics of the included studies in APS II and III are summarized in Supplementary table 2.

Characteristics of the patients

Distinction between APS II and APS III was made in 842 cases, of which 177 and 665 were APS II and III (21.1% vs 78.9%), respectively [3, 18-34].

Prevalence of HT, GD and AITD in APS

Among all APS patients (1312 cases), thyroid autoimmune disorders were diagnosed in 739 cases (87.8%). The second and third most prevalent autoimmune diseases were T1DM and AD (523 and 137 cases, respectively) as it is expected from the definitions of APS. HT and GD were diagnosed in 279 and 151 cases, respectively. In 309 cases, the diagnosis was AITDs, without any further characterization. The prevalence of HT, GD and AITD was not significantly different among all APS patients (HT: 35%, 95% CI: 16% - 57% vs. GD: 10%, 95% CI: 1% - 22% vs. AITD: 10%, 95% CI: 0% - 31%, p=0.064). (Fig. 2.) [3, 18-34]. No significant differences were found in APS II patients (HT: 10%, 95% CI: 0% - 35% vs. GD: 2%, 95% CI: 0% - 22% vs. AITD: 39%, 95% CI: 5% - 79%, p=0.183) [21, 23, 24, 26, 28-30]. Among APS III patients, the prevalence of

HT, GD and AITD also did not differ significantly (HT: 45%, 95% CI: 14% - 78% vs. GD: 9%, 95% CI: 0% - 27% vs. AITD: 30%, 95% CI: 1% - 72%, p=0.121) [3, 18-34].

Co-existence of other autoimmune disorders in HT, GD and AITD

In HT patients, three autoimmune endocrinopathies (T1DM, AD and POF), five non-endocrine organ-specific (autoimmune hepatitis, pernicious anaemia, vitiligo, multiple sclerosis and coeliac disease), and two systemic autoimmune diseases (RA and psoriasis) were reported.

In GD patients, three autoimmune endocrinopathies (T1DM, AD and POF), five non-endocrine organ-specific (autoimmune hepatitis, vitiligo, coeliac disease, myasthenia gravis and alopecia), and three systemic autoimmune diseases (SLE, RA and Sjögren's syndrome) were diagnosed.

In AITD patients, three autoimmune endocrinopathies (T1DM, AD and POF), four non-endocrine organ-specific autoimmune disorders (autoimmune hepatitis, pernicious anaemia, vitiligo, and coeliac disease) were published and no systemic autoimmune diseases were found.

The evaluation of co-associated autoimmune disorders is hindered by the lack of proper classification of HT and GD. In this part of the analysis, many cases were transported to the AITD group. The prevalence of the individual autoimmune conditions is demonstrated in Table 1. Only T1DM and AD were found in larger proportion of APS patients, 70.7 and 18.5%, respectively. The prevalence of autoimmune hepatitis, pernicious anaemia, vitiligo, POF, celiac disease and RA was between 1-4%, all the others were rare, <1%.

One, two and more than two other autoimmune disorders were combined with autoimmune thyroid abnormalities in 91.8%, 8% and 0,1% of cases, respectively.

HT, GD and AITDs were reported in dual combinations with other autoimmune disorders in 167, 92 and 419 cases (24.5%, 13.5% and 61.8%), respectively. The prevalence of dual combinations in HT, GD and AITD was not different (HT: 35%, 95% CI: 11% - 63% vs. GD: 10%, 95% CI: 0% - 26% vs. AITD: 29%, 95% CI: 3% - 63%, p=0.186). (Fig. 3) [7,18-34]

Triple combinations were less common in GD and did not differ between HT and AITDs (GD: 3%, 95% CI: 0% - 18% vs. AITD: 77%, 95% CI: 21% - 100%, vs. HT: 14%, 95% CI: 0% - 66% p=0.028) (Fig. 4) [22, 24-28, 31].

More than two autoimmune disorders were never combined with GD and AITD, this clinical situation only occurred in HT, however the low number of cases did not allow a relevant statistical analysis [28, 29, 34].

In HT patients, the most common associated disorders were T1DM, autoimmune hepatitis and pernicious anaemia, in 121, 23 and 19 cases, respectively. GD most commonly manifested together with T1DM, AD and vitiligo (64, 7 and 6 cases, respectively). In the not specified AITDs group, T1DM, AD and vitiligo were the most common combinations (282, 104 and 16 cases, respectively).

The pattern of non-endocrine dual combinations of autoimmune disorders was slightly different between GD and HT; systemic autoimmune disorders – SLE, Sjögren's syndrome and rheumatoid arthritis -, occurred in dual combinations only with GD. In HT patients, systemic autoimmune disorders (RA and psoriasis) were only the part of triple and even more combinations.

Of the non-endocrine organ-specific autoimmune disorders, myasthenia gravis and alopecia occurred in dual combinations only with GD, pernicious anaemia with AITD, and vitiligo with HT. Interestingly, triple combinations of any kind of autoimmune

disorders occurred in GD only in APS II patients. Triple combinations in AITD patients were only detected when T1DM was one of the associated diseases.

Discussion

The combinations of autoimmune disorders are common, however the manifestation of the second or third autoimmune condition may be many years after the presentation of the first disease [35]. The prediction of future autoimmune diseases is difficult; many attempts are based on the screening of autoantibodies [36]. Regular screening procedures are expensive and their cost-effectivity is questionable. Both GD and HT are among the most common autoimmune diseases [36]. In this systematic review and meta-analysis we tried to establish typical patterns of co-associated conditions in HT and GD to help the better orientation of patients and physicians and to initiate a screening algorithm.

The best-characterized combinations of autoimmune disorders are the APS patients [1]. A difference in the prevalence of HT, GD and AITDs could neither be observed in APS II nor in APS III. Co-associated organ-specific endocrine and non-endocrine and systemic autoimmune disorders occurred in both HT and GD. Common co-morbidities were only T1DM and AD, the prevalence of other autoimmune disorders was $\leq$4%. This must be considered when developing cost-effective screening algorithms.

The occurrence of dual combinations was similar in HT, GD and AITDs but triple combinations were less common in GD. Three or more autoimmune disorders were only with combined HT. Systemic autoimmune diseases were present in dual combination with GD, and in triple or more combinations with HT.

Many systemic autoimmune diseases can be associated with AITDs [19, 37]. Organ specific, non-endocrine autoimmunities (such as pernicious anaemia, coeliac disease, autoimmune hepatitis, multiple sclerosis, and myasthenia) are also common comorbidities. This means that proper screening protocols for AITDs may be useful in patients with systemic autoimmunities as well as with organ specific autoimmune

diseases [37]. Unfortunately, studies investigating the association of non-endocrine autoimmune disorders did not specify HT and GD in the majority of AITD patients [19, 37]. These associations would be more interesting if there would be a proper distinction between HT and GD.

A previous review found that HT is significantly more frequent in individuals who suffer from other autoimmunities, such as AD, T1DM, RA or SLE [36]. In our meta-analysis, T1DM, autoimmune hepatitis, pernicious anaemia, POF, AD, vitiligo, coeliac disease, MS, RA and psoriasis were found in HT patients.

A recent study showed that in GD patients, the following autoimmune diseases were observed with a significantly higher prevalence: T1DM, celiac disease, autoimmune gastritis, vitiligo, RA, Sjögren's syndrome, SLE, sarcoidosis, hepatitis C virus - related mixed cryoglobulinemia, polymyalgia rheumatica and multiple sclerosis [38, 39]. In our review, T1DM, POF, AD, autoimmune hepatitis, vitiligo, coeliac disease, myasthenia gravis, alopecia, SLE, RA and Sjögren's syndrome was diagnosed in GD patients. Interestingly, in GD patients, triple combinations occurred only when AD was one of the associated disorders.

HT and GD are both due to polymorphisms of the HLA DQ/DR regions [13]. Immune-regulatory genes such as HLA region, CD40, CTLA4, PTPN22, and FCRL3 are involved in the pathogenesis of GD [39]. Protective genes such as HLA-DRB1* 07, HLA-C03, and HLA-C*16 have also been identified. CTLA4 polymorphisms are associated with an increased risk of GD and HT [13]. HT has been found strongly associated with HLA haplotypes DRB1*03:01, -DR4, -DR5, and -DQB1*03:01 (DQ7) [40]. Identification of polymorphisms in immune regulatory genes may be useful to estimate the risk of HT, GD and other combined autoimmunities in APS.

Limitations of the study

Unfortunately, publications in the field of APS are mainly case reports, only 18 retrospective and cohort studies were suitable for further analysis and the number of published APS patients was low. Although AITDs are the most common autoimmune disorders in APS (87.8%), only 739 AITDs patients were collected with known co-associations of other autoimmunities. Moreover, only 58% of patients were initially classified as HT or GD and even this classification became confused during the discussion of combinations, so only 39% of patients was available for analysis of autoimmune combinations. This limits the potential conclusions and raises our attention to the necessity of better documentation.

Strengths of the study

This is the first systematic review and meta-analysis in the field of APS and the first attempt to establish typical patterns of co-associated autoimmune conditions in HT and GD. Relevant statistical analysis could be performed despite the limitations.

Implications for practice

The combination of autoimmune disorders is common, and the prediction of multi-organ involvement is important both for the patients and the clinicians. Better and more uniform classification of the clinical data and the development of registries could help to improve the management of patients.

Implications for research

The lack of differences between HT and GD in the association of other autoimmune disorders indicates similarities in the immunological background. As the genetic predisposing factors are seemingly heterogeneous, the investigation of genetic polymorphism may serve the classification of patients and have prognostic significance.

In conclusion, using a systematic review and meta-analysis, no difference in the prevalence of HT and GD was found in APS patients and the pattern of co-associated autoimmune disorders was also similar. Many organ-specific endocrine and non-endocrine and systemic autoimmune disorders may occur in patients with autoimmune thyroid disorders, however only T1DM and AD have been reported with high prevalence in APS patients.

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Author contributions

Gréta Pham-Dobor and Emese Mezősi conceptualized and designed the study in cooperation with Péter Hegyi and Katalin Márta; Gréta Pham-Dobor, Marin Gergics and Katalin Márta constructed the forms to be filled with patient data; Gréta Pham-Dobor and Marin Gergics performed the data extraction from the articles. Gréta Pham-Dobor wrote the article; Emese Mezősi supervised the study. Emese Mezősi, Péter Hegyi, Patrícia Sarlós, Bálint Erőss, Katalin Márta, Andrea Párniczky, Marin Gergics and Lilla Hanák provided valuable feedback after critically reviewing the first drafts of the manuscript. Lilla Hanák carried out the statistical analysis. All the authors reviewed and approved the final manuscript for publication.

Completing Interests

The authors declare that they have no completing interests.

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Figure legends

Figure 1. PRISMA flow diagram of the study

Figure 2. Prevalence of Hashimoto's thyroiditis, Graves' disease and autoimmune thyroid disorders among autoimmune polyglandular syndrome patients; The prevalence of Hashimoto's thyroiditis, Graves' disease and autoimmune thyroid disorders was not significantly different among all autoimmune polyglandular syndrome patients, ES: effect size

Figure 3. Prevalence of dual combinations in Hashimoto's thyroiditis, Graves' disease and autoimmune thyroid disorder patients; The prevalence of dual combinations in Hashimoto's thyroiditis, Graves' disease and autoimmune thyroid disorder did not reach the level of significance; ES: effect size

Figure 4. Prevalence of triple combinations in Hashimoto's thyroiditis, Graves' disease and autoimmune thyroid disorder patients; The difference in the number of two associated disorders between autoimmune thyroid disorders and Graves' disease was also significant, however it did not reach the level of significance among Hashimoto's thyroiditis patients; ES: effect size

Table 1. The prevalence of other autoimmune disorders associated to any kind of autoimmune thyroid diseases in APS II and III

Autoimmune disorders	**Number of cases**	**Percentages**
Type I diabetes mellitus	523	70,7%
Addison's disease	137	18,5%
Autoimmune hepatitis	31	4%
Pernicious anaemia	28	3,7%
Vitiligo	25	3,4%
Premature ovarian syndrome	21	2,8%
Coeliac disease	20	2,7%
Rheumatoid arthritis	10	1,3%
Alopecia	4	0,5%
Multiple sclerosis	2	0,3%
Systemic lupus erythematosus	2	0,3%
Sjögren's syndrome	2	0,3%
Myasthenia gravis	2	0,3%
Psoriasis	1	0,1%