Patients with a primary diagnosis of autoimmune thyroid disease are at significantly increased risk for additional autoimmune diseases

Boelaert K, Newby PR, Simmonds MJ, Holder RL, Carr-Smith JD, Heward JM, Manji N, Allahabadia A, Armitage M, Chatterjee KV, Lazarus JH, Pearce SH, Vaidya B, Gough SC, Franklyn JA. Prevalence and relative risk of other autoimmune diseases in subjects with autoimmune thyroid disease. Am J Med 2010;123:183.e1-9.

SUMMARY

BACKGROUND

Autoimmune thyroid diseases are common, manifested most commonly as autoimmune thyroiditis (AITD) or Hashimoto's thyroiditis and Graves' disease. The prevalence of spontaneous hypothyroidism is as high as 2% in iodine-replete areas such as the United States and Europe. In addition, autoimmune thyroid diseases are associated with a variety of other disorders such as type 1 diabetes mellitus, Addison's disease, systemic lupus erythematosus, and pernicious anemia, and also appear as a family trait that tends to be associated with many other autoimmune disorders. The object of this cross-sectional multicenter study was to systematically quantify the prevalence of coexisting autoimmune disorders.

METHODS

Data were obtained from a protocol in the national U.K. collection of DNA for studies of genetic susceptibility to autoimmune thyroid diseases, including prospective and systematic collection of clinical data regarding the coexistence of other common autoimmune disorders in index cases and their parents. Patients were recruited from February 2002 through July 2007. The diagnosis of autoimmune disorders was based on patient recall, with confirmation in the index case through verification of current medical records and medications by recruiting physicians. Records confirming the evidence of coexisting autoimmune diseases were considered positive. All subjects completed a structured questionnaire seeking a personal and parental history of common autoimmune disorders, as well as a history of hyperthyroidism or hypothyroidism among parents.

RESULTS

The Prevalence of Coexisting Autoimmune Diseases in Men and Women (Figures 1 and 2)

The study cohort comprised 3286 individuals, 2791 (85%) of whom were white subjects with Graves' disease, 2317 women (83%) and 474 men (17%), and 495 white subjects with Hashimoto's thyroiditis (15%), 427 women (86%) and 68 men (14%) who were recruited from specialist referral thyroid clinics in the United Kingdom. Approximately 90% of the eligible patients participated in the study. The mean age at the time diagnosis was 43 years for the index cases of Graves' disease, and 42.5 years for Hashimoto's thyroiditis (P = not significant [NS]). The mean age at the time of recruitment in the study was not different in the index cases of Graves' disease (47.3 years) or Hashimoto's thyroiditis (47.5 years, P = NS) (Figures 1 and 2). There also were no significant differences in age at the time of diagnosis or recruitment to the study in patients with Graves' disease or Hashimoto's thyroiditis with no coexisting autoimmune disease or for those with an additional autoimmune disorder (Figures 1 and 2).

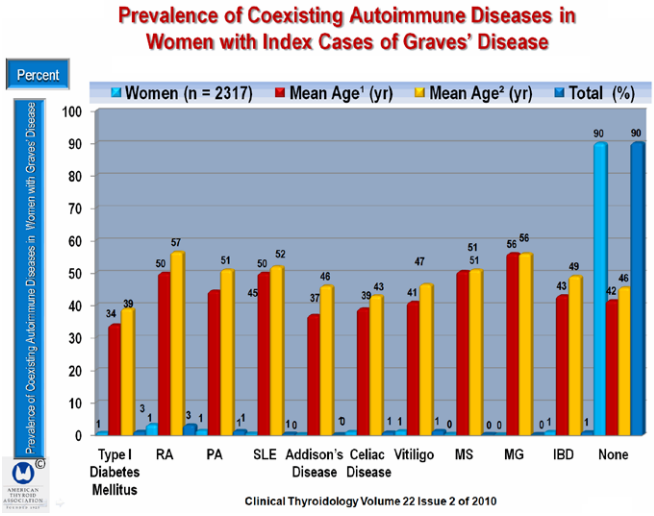

Figure. 1. This figure shows the prevalence of coexisting autoimmune diseases in the index cases of women with Graves' disease. Age1 = age at the time of diagnosis of Graves' disease or Hashimoto's thyroiditis; Age2 = age at recruitment to the study; celiac = celiac disease; IBD = inflammatory bowel disease; MG = myasthenia gravis; MS = multiple sclerosis; PA = pernicious anemia; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus. This figure is drawn from data in Table 2A in Boelaert et al.

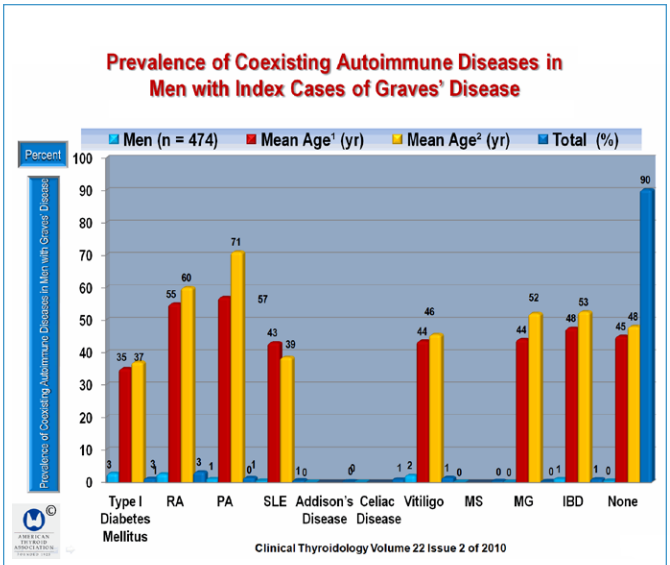

Figure 2. This figure shows the prevalence of coexisting autoimmune diseases in the index cases of men with Graves' disease. (See Figure 1 for definitions of the abbreviations.) This figure is drawn from data in Table 2B in Boelaert et al.

The Prevalence of Coexisting Autoimmune Diseases in the Index Cases with Graves' disease or Hashimoto's Thyroiditis (Figures 3 to 6)

Almost 10% of the 2791 subjects with Graves' disease and 14% of the 495 with Hashimoto's thyroiditis had another autoimmune disorder (P = 0.005). The most common autoimmune disease associated with the index cases of Graves' disease or Hashimoto's thyroiditis was rheumatoid arthritis (Figures 1 and 2). Those with Hashimoto's thyroiditis had a 10-fold higher risk for Addison's disease (P<0.001) and a 3-fold higher risk for pernicious anemia (P = 0.004), as compared with index cases of Graves' disease (Figures 1 and 2). Comparing index cases of Graves' disease, there were significantly higher prevalence rates of type 1 diabetes mellitus (P = 0.011) and myasthenia gravis (P = 0.001) in men as compared with women; however, Addison's disease, celiac disease, and multiple sclerosis were exclusively associated with the index cases of Graves' disease in women. There were no significant differences in the prevalence rates of other autoimmune disorders in men and women with index cases of Hashimoto's thyroiditis (Figures 4 to 6). Comparing male and female patients, there were no significant differences in age at either diagnosis or recruitment. When comparing age at diagnosis of Graves' disease between index cases with different autoimmune diseases (Figure 1 to

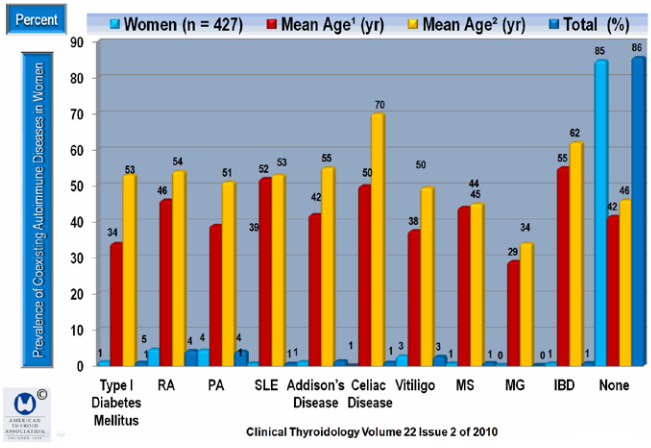

Figure 3. This figure shows the prevalence of coexisting autoimmune diseases in the index cases of women with Hashimoto's thyroiditis disease. (See Figure 1 for definitions of abbreviations.)This figure is drawn from data in Table 2B in Boelaert et al.

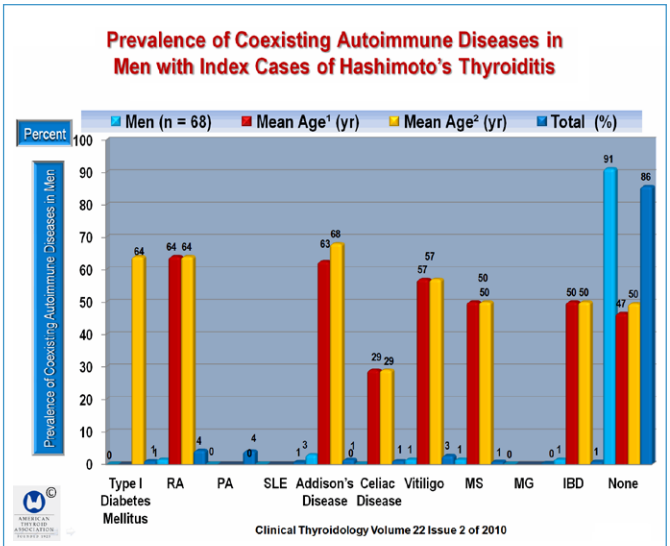

Figure 4. This figure shows the prevalence of coexisting autoimmune diseases in the index cases of men with Hashimoto's thyroiditis disease. (See Figure 1 for definitions of the abbreviations.)This figure is drawn from data in Table 2B in Boelaert et al.

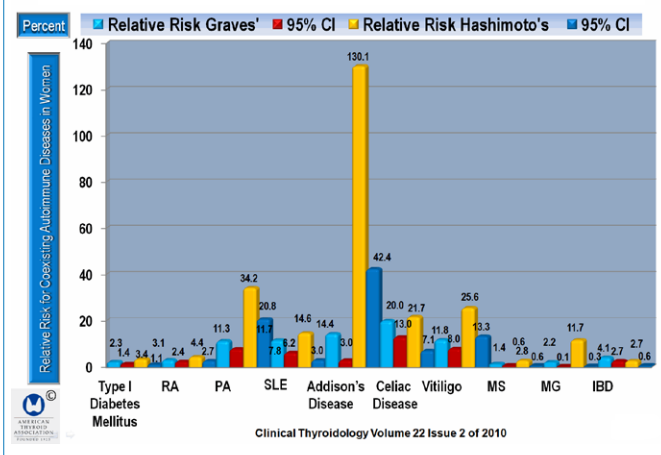

Figure 5. This figure shows the relative risk for a diagnosis of other autoimmune diseases women with index cases of Graves' disease or Hashimoto's thyroiditis. (See Figure 1 for definitions of the abbreviations.) This figure is drawn from data in Table 4A in Boelaert et al.

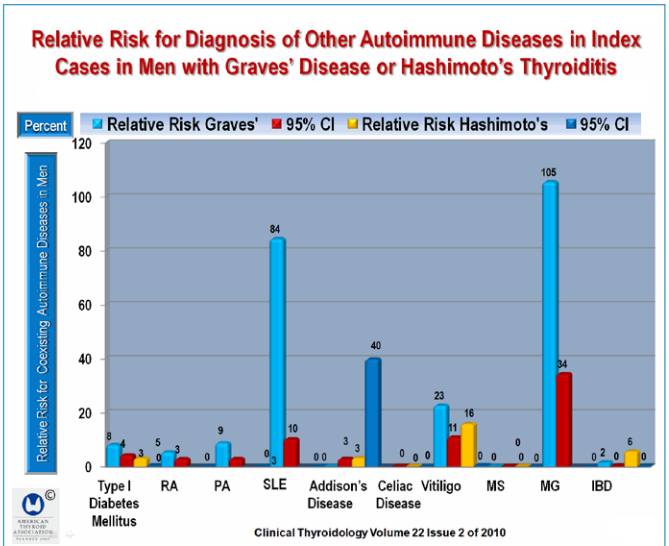

Figure 6. This figure shows the relative risk for a diagnosis of other autoimmune diseases in women with index cases of Graves' disease or Hashimoto's thyroiditis. (See Figure 1 for definitions of the abbreviations.) This figure is drawn from data in Table 4B in Boelaert et al.

4), those with coexisting rheumatoid arthritis were significantly older as compared with patients with no coexisting autoimmune diseases (P<0.001), which was also the case in patients with type 1 diabetes (P<0.001), vitiligo (P<0.001), or inflammatory bowel disease (P = 0.003). Also, subjects with coexisting pernicious anemia were older as compared with index cases with no associated autoimmune disease (P = 0.04) and those with coexisting type 1 diabetes (P = 0.03).

The Prevalence of Coexisting Autoimmune Diseases in parents of Patients with Graves ' disease and Hashimoto's Thyroiditis

A total of 17.5% of the mothers of the index cases with Graves' disease and 23.6% of the mothers of the index cases of Hashimoto's thyroiditis had a history of thyroid dysfunction. The mothers of index cases with Graves' disease were reported to have hyperthyroidism and hypothyroidism with similar frequency (P = NS); however, the mothers of index cases with Hashimoto's thyroiditis had a higher frequency of hypothyroidism than hyperthyroidism (P<0.001). Furthermore, the mothers of index cases with Graves' disease were more likely to have hyperthyroidism (P<0.001) as compared with the mothers of those with Hashimoto's thyroiditis (P<0.001). Hypothyroidism was more common in mothers of patients with Hashimoto's thyroiditis than in mothers of those with Graves' disease (P<0.001).

A total of 3.1% and 5.7% of the fathers of index cases with either Graves' disease or Hashimoto's thyroiditis, respectively, had thyroid dysfunction. Fathers of the index cases with Graves' disease were more likely to have hyperthyroidism than hypothyroidism (P = 0.017), while fathers of the index cases with Hashimoto's thyroiditis more frequently had hyperthyroidism than hypothyroidism (P = 0.007). In all of the autoimmune diseases investigated, except myasthenia gravis, Graves' disease and Hashimoto's thyroiditis and inflammatory bowel disease in Hashimoto's thyroiditis were more commonly found in parents of patients with autoimmune thyroid disease than that in the background U.K. population.

CONCLUSION

Patients with a primary diagnosis of autoimmune thyroid disease are at significantly increased risk for additional autoimmune diseases. The authors of the study suggest that these risks highlight the importance of screening for other autoimmune diagnoses if patients with autoimmune thyroid disease present with new or nonspecific symptoms.

COMMENTARY

This is perhaps the largest study to quantify the risk for coexisting autoimmune diseases in more than 3000 index cases with well-characterized Graves' disease or Hashimoto's thyroiditis. The authors point out that this study demonstrated the high relative risks for the diagnosis of several organ-specific autoimmune disorders, particularly pernicious anemia, Addison's disease, and celiac disease. In addition, they demonstrated parental clustering of index cases of hyperthyroidism and hypothyroidism. The authors indicated that the higher prevalences and relative risks of rheumatoid arthritis in parents as compared with index cases suggest a strong disease association in the two. The index cases with coexisting rheumatoid arthritis were older at diagnosis of Graves' disease, and the authors suggest that it is possible that the same age-related autoimmune mechanisms contribute to the pathogenesis of both of these autoimmune diseases. There also was a striking association between autoimmune thyroid diseases and Addison's disease, although the authors caution that this apparent association may have been exaggerated by the influence of Addison's disease on thyroid function caused by a well-described phenomenon of increasing serum thyroid-stimulating hormone in untreated glucocorticoid deficiency that might lead to an incorrect diagnosis of hypothyroidism. One of the main findings in this study was that the frequency of coexisting autoimmune disorders was nearly 10% in the index cases of Graves' disease and almost 15% in the index cases of Hashimoto's thyroiditis (P = 0.005). Rheumatoid arthritis was the most common autoimmune disorder, found in over 3% of patients with Graves' disease and over 4% of patients with Hashimoto's thyroiditis.

The authors provide the caveat that screening for other autoimmune diagnoses might be indicated if patients with autoimmune thyroid disease present with new or nonspecific symptoms. They further propose additional investigation of susceptibility genes common to more than one autoimmune disorder.

Several years ago, Allen et al. (1) studied autoimmune thyroiditis in a homogeneous founder white population, the Old Order Amish of Lancaster County in Pennsylvania, and found that circulating antimicrosomal antibodies were relatively common in the Amish, with a prevalence of almost 23%, and the prevalence of autoimmune hypothyroidism was nearly 10%. The authors found suggestive evidence of linkage of autoimmune thyroid disease confined to a locus on chromosome 5q11.2-q14.3 that was previously reported to be linked to AITD–hypothyroidism in a Japanese study. The authors suggested that this gene is likely to contribute to the susceptibility to autoimmune thyroiditis in the Amish. Other studies (2) have found subclinical autoimmune thyroid disorders in patients with systemic sclerosis, type 1 diabetes mellitus, celiac disease (3-6), and other diseases (3-9).

The study by Boelaert et al. is a significant contribution that provides important new information on this problem

— Ernest L. Mazzaferri, MD, MACP

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