Clin Thyroidol 2013;25:37–39.

Clinical THYROIDOLOGY
AMERICAN THYROID ASSOCIATION
FOUNDED 1923

How Important Are Preexisting Comorbidities and Genetic Proclivities in Explaining the Increased Risk of Mortality in Hyperthyroidism?

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Brandt F, Almind D, Christensen K, Green A, Brix TH, Hegedüs L. Excess mortality in hyperthyroidism: the influence of preexisting comorbidity and genetic confounding: a Danish nationwide register-based cohort study of twins and singletons. J Clin Endocrinol Metab 2012;97:4123-9. Epub August 28, 2012; doi: 10.1210/jc.2012-2268.

SUMMARY

Background

Patients with hyperthyroidism have an increased risk of mortality. Clearly the associated atrial fibrillation, coagulopathies, and thromboembolism can increase mortality, but the importance of preexisting diseases and of different genetic backgrounds remain to be established. The authors report a retrospective population-based study, using a variety of Danish databases, to begin to address some of these issues.

Methods

All twins born in Denmark since 1954 have been entered in a twin registry, and the vital status and cause of death for everyone in Denmark has been recorded since 1968. Since 1977, all hospital discharge International Classification of Diseases, 8th (ICD8) or 10th (ICD10) Revision diagnoses—and since 1995, the ICD diagnoses for all outpatient hospital clinic visits and all purchases of antithyroid drugs—have also been recorded. The authors randomly selected 5% (339,481) of all patient records, and then excluded about 60,000 patients who were under 18 years of age or had died before 1977. From the remainder, all who had been given one of the ICD codes for hyperthyroidism and/or who had purchased antithyroid drugs at least twice since 1995 were identified, and the cause of death (or survival up to the end of 2008) was determined. Hyperthyroidism was found in 4850 patients who had been single births. From the twin registry, hyperthyroidism was identified in 926 same-sex twins, and 625 had a twin pair who did not have hyperthyroidism up to 2008. Four controls, matched for age and sex, were obtained for each singleton with hyperthyroidism, while for each twin with hyperthyroidism, four nonrelated non-control twins who did not have hyperthyroidism, matched for age, sex, and zygosity, were obtained. The Charlson comorbidity index—a weighted sum for 19 common medical conditions, which predicts 1-year mortality—was calculated for each patient and control, based on ICD codes. Pearson chi-square tests were used to compare group frequencies, t-tests to test group means, Mann–Whitney tests for group medians, and paired t-tests for paired comparisons.

Results

Each group with hyperthyroidism had more comorbidity than its control group. The risk for mortality in the 4850 singleton patients with hyperthyroidism was increased by 37% (hazard ratio [HR], 1.37; 95% confidence interval [CI], 1.30 to 1.46), as compared with their controls over a mean of 10 years of follow-up. After adjusting for sex and comorbidity, essentially the same results were obtained. The 2065 singleton patients with hyperthyroidism who had no documented comorbidity before their hyperthyroidism had been diagnosed still had an increased risk for mortality (HR, 1.28; 95% CI, 1.21 to 1.36), suggesting the hyperthyroidism was directly associated with the increased mortality.

In the 625 twin pairs discordant for hyperthyroidism, the HR for mortality was 1.43 (95% CI, 1.09 to 1.88),

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as compared with the euthyroid sibling, over a mean follow-up period of 10.5 years. A similar increase was found when the twin with hyperthyroidism was compared with its four control twins. In the 418 same-sex dizygous twin pairs, the HR was 1.80 (95% CI, 1.27 to 2.55), as compared with the euthyroid sibling. In marked contrast, when the 201 monozygous twin pairs were compared, the mortality in the sibling with hyperthyroidism was not significantly different from that of the unaffected sibling. When the 413 twins who had had no comorbidity prior to the diagnosis of hyperthyroidism were studied, again the dizygous twins with hyperthyroidism still had increased mortality, yet the monozygous twins with hyperthyroidism did not.

Conclusions

In singletons with hyperthyroidism as well as in same-sex dizygous twin pairs discordant for hyperthyroidism, the risk of mortality is increased, independent of any medical conditions documented before the diagnosis of hyperthyroidism was made. In contrast, mortality in same-sex monozygous twins discordant for hyperthyroidism may be more influenced by genetic factors.

ANALYSIS AND COMMENTARY

One might question the validity of lumping twins with Graves' disease together with twins with toxic nodular goiter, because of the well-recognized genetic component of Graves' disease. It therefore is worth noting that Swedish patients hospitalized with toxic nodular goiter were found to have twice the risk of having a sibling who also had toxic nodular goiter, versus the risk of patients hospitalized with Graves' having a sibling with Graves' disease, although the number with toxic nodular goiter was much smaller than the number with Graves' disease (1). Over the 31 years that the Danish data were being recorded, methods of testing, diagnostic criteria, and therapies for many diseases improved, and some of the death codes used and the individuals who performed the coding underwent changes. Furthermore, the relative frequency of different causes of hyperthyroidism in Denmark also changed, since dietary iodine levels and the relative incidence of Graves' disease versus toxic nodules underwent major shifts during the period of the study. In addition, subacute hyperthyroidism and transient hyperthyroidism due to thyroiditis became better recognized. Another issue is the possibility that hyperthyroidism was induced in patients with preexisting cardiovascular conditions when iodine-containing drugs or contrast agents were administered. The assessment of comorbidities may also be incomplete, since some diseases known to be associated with hyperthyroidism, as well as some complications known to be produced by therapies for hyperthyroidism, might not have been noted in the Charlson score, as it is based on only 19 common diseases.

Information concerning thyroid-function tests, therapies used, the period between diagnosis and restoration of euthyroidism, recurrences, and so forth was not available. It might have been instructive to show the survival curves after hyperthyroidism was diagnosed, in view of earlier studies showing that the excess mortality after treatment with radioiodine occurred mostly in the first year (2), and also to look for possible time trends in the causes of mortality.

Notwithstanding these caveats, such studies are very difficult to do, and are important if we are to eventually understand why (and when) patients with hyperthyroidism are at increased risk of mortality.

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