Association of Hypothyroidism and Obstructive Sleep Apnea

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Obstructive sleep apnea (OSA) and hypothyroidism are relatively common disorders that have similar clinical features and are thought to be causally linked. We sought to determine the prevalence of previously unrecognized hypothyroidism in a series of patients evaluated for OSA and whether an association between hypothyroidism and OSA was present. Chart review was used to obtain information on thyroid function status, polysomnography results, levothyroxine use, and clinical signs and symptoms in 336 consecutive adult patients who underwent polysomnography for suspected OSA. In addition, levothyroxine use was determined in age- and sex-matched control subjects for the purposes of a case-control study. Among the patients without prior history of hypothyroidism who underwent polysomnography and thyroid function testing, four new cases or 1.41% (95% CI 0.04–2.78) were found to have subclinical hypothyroidism. Our findings do not support routine thyroid screening by specialists in patients referred for polysomnography. The odds ratio of the association of prior history of hypothyroidism to OSA was 1.47 (95% CI 0.8–2.8). Limitations in study design may have limited our ability to detect a statistically significant association between OSA and hypothyroidism. Kapur VK, Koepsell TD, deMaine J, Hert R, Sandblom RE, Psaty BM. Association of hypothyroidism and obstructive sleep apnea. AM J RESPIR CRIT CARE MED 1998;158:1379–1383.

Obstructive sleep apnea (OSA) is a common disorder in which sleep-disordered breathing causes disrupted sleep as well as other sequelae (1–6). Patients with OSA often present with symptoms of excessive daytime somnolence, apathy, and lethargy, all of which can be seen in individuals with another common disorder, hypothyroidism. This similarity in presenting symptoms raises a question on how patients with suspected OSA should be evaluated. Should all individuals suspected of having OSA also be evaluated for hypothyroidism? Authors have made conflicting recommendations on this issue (7–10).

In addition, an etiologic relationship between hypothyroidism and OSA has been hypothesized for some patients. The mechanisms proposed to explain how hypothyroidism might cause OSA include mucoprotein deposition in the upper airway, decreased neural output to the upper airway musculature, obesity, and abnormalities in ventilatory control (7, 11, 12–15). Case series have reported that 50 to 100% of patients with hypothyroidism and OSA show a reduction in sleep-disordered breathing with levothyroxine therapy, though not always of a sufficient degree to eliminate OSA.

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The issue of an association between these disorders has been approached in two ways. In patients with hypothyroidism, disordered breathing appears to be very common; yet in patients with OSA, hypothyroidism is very uncommon (7, 8, 11, 12–16). There has not been an unequivocal demonstration of a significant association between these disorders.

In order to address these issues of association and clinical practice, this study examined a large case series of consecutive patients referred for polysomnography who were also evaluated for hypothyroidism. In this study, we estimated the prevalence of hypothyroidism diagnosed at time of initial sleep evaluation and gave details on clinical features and outcomes in these subjects. To measure the association of hypothyroidism with OSA, a case-control study was also conducted.

METHODS

Study Design

The cross-sectional study used information obtained as a part of routine clinical practice in a health maintenance organization (HMO) to determine the prevalence of undiagnosed hypothyroidism. The case-control study used population controls to assess the association of OSA with a prior history of hypothyroidism. The protocol for this study was approved by the institutional review boards of Group Health Cooperative (GHC) and the University of Washington.

Setting

Group Health Cooperative of Puget Sound is a staff model HMO with 388,000 members in western Washington State which provides the full spectrum of specialty services through its own salaried professional staff to its enrollees. The enrollee population at GHC is comparable to the surrounding community with respect to race, but it has fewer individuals at the extremes of income (17). Subjects included in this study sought routine care at one (East) of four regions served by this

HMO. The East region had approximately 100,000 members during the period of this study. Referral for sleep-related complaint was at the discretion of GHC primary care providers who generally referred patients with suspected OSA to a pulmonologist and patients with primary complaints of snoring to an otolaryngologist. Thyroid function testing was a routine part of the workup of patients suspected of having OSA during this period.

Subjects

The records of all patients evaluated for suspected OSA from the East Region of GHC between January 1, 1991 and January 30, 1994 and subsequently referred for polysomnography were reviewed. A total of 336 adult ($\geq$ 18 yr old) patients with no prior history of OSA at the time of initial visit for a sleep-related complaint were included in our study.

Controls

A control group consisting of 1,713 subjects of similar age, sex, region, and duration of enrollment to the case series of patients was assembled at random from the GHC membership database.

Data Collection

Demographic data, general medical history (including history of hypothyroidism), clinical information from visits for sleep-related complaints, as well as results of thyroid function testing and polysomnography results for subjects were abstracted from medical records. Preexisting hypothyroidism was defined as having an elevated thyroid-stimulating hormone (TSH) level more than 1 mo preceding the initial visit, or in the absence of an elevated TSH level, the documentation of an iatrogenic cause of hypothyroidism (thyroidectomy, radioactive iodine therapy) or a clinical presentation (fatigue, cold intolerance, bradycardia) consistent with hypothyroidism which improved with replacement therapy

Patients found to have an elevated TSH level within 1 mo of initial sleep evaluation had additional review of their medical records to determine clinical presentation at initial evaluation and response to thyroid replacement. These patients were considered previously unevaluated cases if the diagnosis of hypothyroidism was confirmed by the corroboration of thyroid status during repeat testing (elevated TSH levels prior to thyroid replacement or normal levels during replacement).

The population-based computer pharmacy database at GHC provided information on levothyroxine use for all subjects and controls. Virtually all GHC enrollees have significant coverage for prescription medications when filled through a GHC pharmacy. Methodological studies have indicated that over 90% of prescriptions are filled through GHC pharmacies (18). Subjects taking thyroid replacement at any time during the 2 yr prior to the year of the initial sleep visit were classified as having preexisting hypothyroidism. Because pharmacy data were available only since 1990 for subjects, pharmacy data from 1990 alone were used for individuals seen in 1991. Among control subjects, individuals with a record of levothyroxine use in 1991 or 1992 were classified as having preexisting hypothyroidism.

Thyroid Testing

TSH concentrations and free T4 (FT4) concentrations were determined in the GHC clinical laboratory using sensitive radioimmunoassay techniques. The normal range for TSH in the GHC laboratory is 0.7 to 6.0 mIU/L. The normal range for FT4 is 0.6 to 1.8 ng/dl.

Polysomnography

Standard polysomnographic studies were performed and scored in an American Sleep Disorders Association (ASDA)-certified laboratory. Subjects with an apnea–hypopnea index (AHI) $\geq$ 10 or a primary diagnosis of OSA on the polysomnography report were classified as having OSA.

Data Analysis

Chart review and pharmacy data, using the criteria for preexisting hypothyroidism stated earlier, were used to obtain two measurements of the prevalence of prior hypothyroidism among subjects. The accuracy of using pharmacy data to ascertain history of hypothyroidism was determined, using the results of chart review as the "gold standard." The prevalence of hypothyroidism among control subjects based on pharmacy data was also calculated.

A case-control comparison to evaluate the association of prior hypothyroidism with the presence of OSA was performed. Cases consisted of subjects meeting our stated criteria for OSA. The controls have been previously described. The exposure, a history of hypothyroidism, was defined on the basis of pharmacy data indicating thyroxin use. A crude odds ratio and 95% confidence intervals were calculated. Cases and control subjects were stratified by age ($\geq$ 50 or $<$ 50 yr) and gender. Stratum-specific odds ratios and 95% confidence intervals were determined. These strata were compared using the chi-square test for heterogeneity. A summary odds ratio using the Mantel-Haenszel method was calculated.

RESULTS

Description of Subjects

The 336 subjects were referred for polysomnography after an evaluation by a specialist in the vast majority of cases (91.4%), though a small number (8.6%) were referred after initial evaluation by family practice or internal medicine. The three most frequented specialties were pulmonary (56.5%), otolaryngology (25.0%), and neurology (6.3%). The group was composed predominantly of males (78%) and had a mean age of 52 and mean weight of 102 kg. A history of snoring (99%), witnessed apneas (89%), or daytime somnolence (73%) was present in the majority of subjects who had information concerning these signs and symptoms of OSA available in the initial visit note. The subjects had a high prevalence of common chronic illnesses noted in the medical record including: hypertension (35%), depression (21%), asthma (16%), diabetes mellitus (12%), and coronary artery disease (11%).

A total of 301 subjects had a TSH test or a documented history of hypothyroidism at the time of initial evaluation. The remaining 35 subjects, who had no laboratory data on thyroid hormone status, were different from the 301 individuals in several ways. They were more likely to be male, weigh less, and have been seen initially by an otolaryngologist (63%) rather than a pulmonologist (20%). They were also less likely to have a record of a complaint of daytime somnolence or have coronary artery disease, congestive heart failure, diabetes mellitus, or hypertension.

Previously Diagnosed Hypothyroidism

Seventeen subjects were noted to have previously diagnosed hypothyroidism at the time of initial evaluation (17 of 336 = 5.1%; 95% CI 3.1–7.1) by chart review. This number is the same obtained by review of pharmacy data in the 2 yr prior to the initial visit, though pharmacy data only identified 14 of 17 subjects identified by chart review plus three additional subjects not identified by chart review to give a sensitivity of 82.4% and specificity of 99.1% (*see* Table 1).

The number of years prior to initial visit that hypothyroidism was noted to be present ranged from 5 mo to 22 yr and 15

TABLE 1

ACCURACY OF PHARMACY DATA IN CLASSIFYING HYPOTHYROIDISM

Pharmacy Data	Hypothryoidism Confirmed	Hypothyroidism Not Confirmed	Total
Thyroxin use	14	3	17
No thyroxine	3	316	319
Total	17	319	336

Sensitivity = 82.4%; specificity = 99.1%.

subjects were diagnosed more than 2 yr prior to presentation with a sleep complaint. Nine hypothyroid subjects either had no clinical features suggestive of hypothyroidism at the time of its original diagnosis and were presumably detected by routine thyroid function testing or had no medical records available from that time. Four hypothyroid subjects had a history of an iatrogenic cause (thyroidectomy or radioiodine therapy) and four hypothyroid subjects were noted to have signs or symptoms consistent with hypothyroidism at the time the diagnosis was initially made.

The prevalence of hypothyroidism among our control subjects was 3.9% (95% CI 2.9–4.9).

Previously Undiagnosed Cases of Hypothyroidism

Based on testing performed during or after the initial visit for a sleep complaint, four subjects were found to have previously undiagnosed hypothyroidism (4 of 284 = 1.41%; 95% CI 0.04–2.78). None of the four had symptoms or signs other than fatigue and snoring noted at the time the testing was ordered. All four subjects had normal free T4 concentrations and minor elevations of TSH (range 6.3 to 12.1; normal < 6.0) putting them in the category of subclinical hypothyroidism. Two subjects were male and two were female; their ages ranged from 27 to 64, and their AHIs from 6 to 30.4. Two of the four subjects had a family history of hypothyroidism noted in the chart.

Three of the patients in whom hypothyroidism was newly diagnosed received therapy with thyroxin. Only one of the three had subjective improvement noted in the medical record that was attributed to thyroxin replacement.

The mean age and gender composition of newly evaluated and previously evaluated cases were compared with those of patients who did not have hypothyroidism (Table 2). Patients with hypothyroidism were significantly more likely to be female.

Association of OSA with Hypothyroidism

The presence of prior hypothyroidism among cases with OSA and control subjects stratified by age and gender is given in Table 3. The crude and stratum-specific odds ratios did not reveal a statistically significant association between prior hypothyroidism and OSA. The odds ratios differed in magnitude for different strata, but were not statistically significant by the Chi-square test for heterogeneity. The association of hypothyroidism to OSA was greater in females and in those less than 50 yr of age. The summary odds ratio after stratification for age and gender was 1.47.

DISCUSSION

Prevalence of Undiagnosed Hypothyroidism and of Previously Diagnosed Hypothyroidism

Our study demonstrated that few new cases of hypothyroidism were discovered as a result of routine thyroid testing in a HMO population undergoing polysomnography for a suspected sleep disorder (4 of 284 = 1.41%, 95% CI 0.04–2.78). Three other studies have estimated the prevalence of hypothyroidism in consecutive patients (61 to 243) evaluated by polysomnography for sleep disorders (7, 8, 16). The prevalence of previously undiagnosed hypothyroidism obtained in these studies (0.7 to 3.1%) was similar to our result.

The prevalence of preexisting hypothyroidism among subjects (5.1%) was higher than the percentage of cases with preexisting hypothyroidism reported in the other two series that have provided this number (0.7 to 0.8%), though it was not much higher than the prevalence of hypothyroidism in our control population (3.9%) (8, 16). This disparity with previous studies may be due to a difference in the population from which referrals for polysomnography came or a bias against referral of patients with treated hypothyroidism in the other studies. The previous studies did not have control populations.

Our study had several strengths which distinguish it from prior published reports of the frequency of hypothyroidism in patients evaluated for sleep disorders. This was the largest series of patients described to date. All 336 subjects had extensive review of chart data including problem and medication lists and laboratory studies to allow a thorough ascertainment of history of previously diagnosed hypothyroidism, an issue that has not been addressed by many previous studies. We had descriptive information on the population from which our subjects were derived and how they were selected. Our subject group consisted of all adult patients referred for polysomnography, regardless of referring specialty from a single district in an HMO with a well-described population. Finally, we had a control group derived from the same HMO from which the cases arose. The prevalence of hypothyroidism was estimated in the same way for cases and control subjects.

A potential pitfall of our study is that patients who were evaluated by a physician for sleep apnea, found to be hypothyroid and subsequently not studied by polysomnography, may have been missed because our study only included subjects who underwent polysomnography. We believe that if there were any such cases, they were very few based on the recollections of the three authors (J.D., R.H., and R.S.) who saw the majority of referrals for sleep apnea in the East Region of GHC during the time period of this study.

The decision of whether to perform routine testing for a disease prior to it being clinically apparent in a group depends on several issues including the severity of consequences of the disease, the advantage of treating the disease before specific signs and symptoms develop, the burden of testing, and the

TABLE 2

PREVIOUSLY UNDIAGNOSED AND PREVIOUSLY DIAGNOSED HYPOTHYROIDISM AMONG PATIENTS REFERRED FOR POLYSOMNOGRAPHY

	Previously Undiagnosed	Previously Diagnosed	Not Hypothyroid
Count	4	17	315
Mean age	45	56	50
% Female*	50%	59%	20%

* Hypothyroid patients more likely to be female ($p < 0.01$).

TABLE 3

HYPOTHYROIDISM AMONG CASES AND CONTROLS STRATIFIED BY AGE AND SEX

Group	Sex/Age	Hypothyroid	Not Hypothyroid	Odds Ratio (95% CI)
Cases	Male, < 50	2	92	1.54
Controls	Male, < 50	7	496	(0.32, 7.55)
Cases	Male, ≥ 50	3	108	0.91
Controls	Male, ≥ 50	22	718	(0.27, 3.09)
Cases	Female, < 50	3	21	2.90
Controls	Female, < 50	10	203	(0.74, 11.36)
Cases	Female, ≥ 50	4	21	1.56
Controls	Female, ≥ 50	28	229	(0.50, 4.87)

Crude odds ratio = 1.22; 95% CI = 0.65– 2.28.
Chi-square test for overall association for strata = 1.98 ($p > 0.10$).
Summary odds ratio = 1.47; 95% CI = 0.77–2.79.

prevalence of undiagnosed disease in the group (18). Our study found the prevalence of undiagnosed hypothyroidism to be fairly low. At this prevalence it would be expected that there would be a significant number of false-positives relative to number of cases detected, resulting in further testing or inappropriate treatment. This, in addition to the cost and discomfort of testing, represents the burden of routine testing.

The benefit of treating the patients who were diagnosed as hypothyroid is debatable. All of the newly diagnosed cases were of the subclinical type and the value of treatment for this type is unclear (19). It is also not known whether subclinical hypothyroidism causes OSA or that its treatment would cure coexisting OSA. Even in patients with overt hypothyroidism and OSA, the effect of thyroid hormone replacement on sleep-disordered breathing has been variable.

One potential advantage of diagnosis of hypothyroidism prior to polysomnography is that polysomnography, an expensive and time-consuming test, might be avoided if the hypothyroid patient's subjective complaints are ameliorated by levothyroxine replacement. Our study cannot adequately answer this question because we have an incomplete assessment of the results of levothyroxine replacement as well as a very small number of new cases. One subject with mild sleep-disordered breathing (AHI = 6) that was not treated with continuous positive airway pressure (CPAP) was noted to have subjective improvement after replacement. This potentially was an individual in whom polysomnography could have been avoided.

Based on our results, at present there is little evidence to support routine thyroid function testing by a sleep specialist prior to polysomnography in patients referred by a primary care provider. A more practical approach may be to limit testing to individuals who fail to show sleep-disordered breathing of sufficient severity to explain symptoms, who do not show satisfactory improvement after effective therapy of sleep-disordered breathing, or in whom hypothyroidism is suspected on the basis of physical exam findings.

Association of Prior Hypothyroidism with OSA

Our study gave an estimate of the risk of OSA in individuals with treated hypothyroidism that was modestly higher (1.47 times) than in individuals who had no history of hypothyroidism. This result was not statistically different from the finding of no association between prior history of hypothyroidism and OSA.

The magnitude of association between prior hypothyroidism and OSA was larger for females and those less than age 50. Women under age 50 with prior hypothyroidism had the highest relative risk (2.9) of OSA, though the association was not statistically significant even for this subgroup.

The ability to ascertain whether or not there is an association between hypothyroidism and OSA in our study is limited by several issues. It was not possible to measure the exposure of perhaps greatest interest, that is, the duration and severity of untreated hypothyroidism. Instead we used an available marker for exposure—a history of thyroid medication use. This could have diluted any true association between hypothyroidism and OSA. In addition, the treatment of hypothyroidism in control subjects, depending on the degree to which it lessened sleep-disordered breathing, could have diminished the association as well. Finally, given the modest magnitude of the odds ratio we obtained, a larger sample size may be needed to exclude the role of chance.

The evidence in humans of an association between OSA and hypothyroidism consists of a number of small case series (11 to 26 patients) that have demonstrated a prevalence of OSA in patients with hypothyroidism ranging from 25 to 82% (7, 11, 13, 15). The only case series with a control population compared the frequency of sleep-disordered breathing in 26 consecutive patients diagnosed with hypothyroidism with 188 randomly selected euthyroid individuals from the general population (15). It found that sleep-disordered breathing as a percentage of total time in bed was higher in hypothyroid patients than in control subjects (50.0 versus 29.3%, $p = 0.04$). Even after adjusting for differences in age, gender, and body mass index (BMI), the association between hypothyroidism and the frequency of sleep-disordered breathing approached statistical significance ($p = 0.06$). The adjustment for differences in BMI between the two groups would have falsely reduced the strength of causal association, if obesity were involved in the causal pathway between hypothyroidism and sleep-disordered breathing.

The published data argue in favor of an association between OSA and hypothyroidism. Our study, which was only able to measure a modest, statistically nonsignificant association between prior history of hypothyroidism and OSA, indicates larger sample sizes and better measures of exposure to hypothyroidism will be needed to unequivocally determine the presence and magnitude of the association.

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