Gender Differences in TRH-Stimulated TSH and Prolactin in Primary Degenerative Dementia and Elderly Controls

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We performed thyrotropin-releasing hormone (TRH) stimulation testing in 18 nondepressed patients with primary degenerative dementia (10 M, 8F; average age ± SD = 68 ± 7) and 12 elderly controls (7M, 5F; average age ± SD = 61 ± 6). Six patients were retested approximately 2 years later. Initial Mini-Mental State Examination scores for patients ranged from 2 to 28 (average ± SD = 18 ± 6) and the scores for the control subjects were all equal to 30. Protirelin (500 μg) was injected iv and blood was sampled at 0, 15, 30, 45, 60, and 90 min for thyrotropin-stimulating hormone (TSH) and prolactin (PRL). There were no significant differences between patients and controls in baseline T4, T3 uptake, TSH, or PRL. No significant differences were found between patients and controls for either TRH-stimulated TSH or PRL at all time points. Duration of illness, severity of dementia, and severity of depressive symptoms did not correlate significantly with stimulation test results. There were, however, significantly greater responses in stimulated TSH and PRL for women compared with men in both patients and controls. Upon repeat testing (n = 6), TRH-stimulated TSH and PRL were not significantly different from the initial results.

Introduction

The thyrotropin-releasing hormone (TRH) stimulation test has been used to test hypothalamic-pituitary axis functioning in a variety of psychiatric disorders. A blunted thyrotropin-stimulating hormone (TSH) response ($\Delta TSH_{max} < 5.0$ μU/ml) has been observed most consistently in approximately 25% of patients with major depression, 50% of alcoholic patients in acute withdrawal, and 30% of alcoholic patients abstinent for more than 2 years (Loosen 1985). Less consistent are TRH stimulation test results in patients with primary degenerative dementia (PDD) when compared with age-matched controls. The rationale for testing hypothalamic-pituitary axis functioning in PDD patients has been based on the finding of senile plaques and neurofibrillary tangles in the hypothalamus (Ishii 1966; McDuff and Sumi 1983). In addition, somatostatin deficiency, which has

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Received September 30, 1989; revised December 27, 1989.

0006-3223/90/$03.50

been found in brain (Davies et al. 1980) and cerebrospinal fluid (CSF) (Raskin et al. 1986) in PDD patients, could produce an enhanced TSH response to TRH stimulation because somatostatin normally inhibits TSH release (Vale et al. 1974). Previous studies have shown no difference in ΔTSH between PDD patients and controls (El Sobky et al. 1986; Franceschi et al. 1988; Lampe et al. 1988; Peabody et al. 1986) or a blunted ΔTSH in patients (Sunderland et al. 1985; Thomas et al. 1987). TRH-stimulated prolactin (PRL) has also been measured and has shown no difference between PDD patients and controls (Thomas et al. 1987), an augmented ΔPRL in patients (El Sobky et al. 1986; Peabody et al. 1986), or a blunted ΔPRL in patients (Newhouse et al. 1986). Because of these inconsistent results, we carried out TRH stimulation testing in nondepressed PDD patients and elderly controls.

Methods

We performed TRH stimulation testing in 18 outpatients who met both DSM-III criteria for PDD and NINCDS/ADRDA criteria for probable dementia. All patients participated in a comprehensive diagnostic assessment that included a physical and neurological examination, neuropsychological testing, screening laboratory evaluations, an electrocardiogram (ECG), and a computed tomography (CT) scan of the head. Exclusion criteria consisted of (1) a history of psychiatric or neurological disorders including substance abuse and major depression, (2) daily psychoactive drug use within the preceeding 4 months, (3) significant physical illnesses including thyroid disorders within the preceeding 4 weeks, and (4) a score of 16 or greater on the 21-item Hamilton Depression Scale (HAM-D). In addition, we carried out TRH stimulation testing in 12 healthy elderly control subjects who had no evidence of a dementing disorder and were free of any significant medical illnesses or psychiatric disorders. The control group was recruited from a group of spouses and friends of the patients with primary degenerative dementia. Potential controls were interviewed to obtain information about significant past and current medical and psychiatric illnesses. Potential controls were excluded if there was any evidence for thyroid dysfunction, e.g., individuals on replacement thyroid medication, recent alcohol abuse, or depression. In both patients and controls all central nervous system (CNS) active medications were tapered and discontinued for at least 4 weeks before performing the TRH stimulation test. Six of the PDD patients were available for repeat TRH stimulation testing, which occurred between 21 and 30 months after the initial study (average interval ± SD = 25 ± 3).

All subjects fasted from midnight until the end of the procedure. After arriving at the hospital in the morning, an indwelling i.v. canula was placed into an arm vein at approximately 8:30 AM and a 9-ml blood sample was taken for baseline T4, T3 uptake, TSH, and PRL immediately after insertion of the i.v. needle (Ferriani and de Sa 1985). Protirelin (500 μg) was injected i.v. at 9:00 AM and 4-ml blood samples were taken for measurement of TSH and PRL at 15, 30, 45, 60, and 90 min following the injection. All subjects were recumbant during the procedure. Samples were centrifuged for 10 min at 2500 rpm; the serum samples were then separated and stored at −20°C for subsequent analyses. Subjects left the hospital after completion of the study.

Both TSH and PRL were assayed by separate double antibody radioimmunoassay (RIA) procedures. The interassay and intraassay coefficients of variation for 5 μIU/ml TSH (Kallestad Laboratories, Inc., Austin, TX) were 10.6% and 5.3%, respectively. The interassay and intraassay coefficients of variation for 7–9 ng/ml PRL (Diagnostic

Products Corp., Los Angeles, CA) were 8.6% and 4.4%, respectively. The clinical laboratory measured baseline T4 and T3 uptake.

To determine differences in overall group response and in the rate of decline of stimulated TSH and PRL (statistical group interaction), repeated measures analyses of variance were done on ΔTSH and ΔPRL levels for the peak response and all succeeding time points. Two-sample *t*-tests were used to compare patient and control values for ΔTSH and ΔPRL at each individual time point. Analyses of covariance (gender X group) with age as the covariate were carried out to examine gender effects while removing the possible influence of age. The areas under the curve (AUC) for TSH and PRL were calculated by adding trapezoidal areas from time zero to the 90-min time point. For those patients who had a repeat TRH stimulation test, matched sample *t*-tests were used to compare ΔTSH and ΔPRL at each individual time point.

Results

The PDD patients (10M, 8F) ranged in age from 55 to 78 (average age ± SD = 68 ± 7) and the control subjects (7M, 5F), from 52 to 72 (average age ± SD = 62 ± 7) ($t = 5.9, p < 0.05$). Mini-Mental State Examination (MMSE) scores ranged from 2 to 28 (average MMSE score ± SD = 18 ± 6) for patients and were all equal to 30 for the controls. The 21-item HAM-D scores in patients ranged from 2 to 10 (average HAM-D scores ± SD = 6 ± 2) and the average duration of illness ± SD was 1.9 ± 2.4 years. The 6 patients (4M, 2F) who were available for repeated TRH stimulation testing were restudied between 21 and 30 months (average interval = 25 ± 3) after the initial evaluation.

There were no significant differences between PDD patients and controls in baseline T4, T3 uptake, TSH, or PRL, all of which were within normal limits. No significant differences were observed between patients and controls for TRH-stimulated ΔTSH (Figure 1) and ΔPRL (Figure 2) at all time points. Only one patient and one control, both men, had a blunted ΔTSH. The AUCs for TSH and PRL did not differ between patients and controls. Duration of illness, severity of dementia (MMSE), and severity of depressive symptoms (HAM-D) did not correlate significantly with the stimulation test results.

There was, however, a significant relationship between gender and stimulated TSH and PRL levels (Table 1). The ΔTSH_{max} peak (30 min) and the ΔPRL_{max} peak (15 min) were significantly greater for women than for men. Similarly, the AUCs for TSH and PRL were significantly greater for women than for men. Five patients, 4 of whom were women, had ΔTSH_{max} levels that were 1 SD above the patient mean; 2 control subjects, a man and a woman, had ΔTSH_{max} levels that were 1 SD above the control mean. In addition, analysis of covariance showed significantly enhanced TSH responsiveness in women compared with men at 15 min [$F(1,25) = 7.9, p < 0.01$], 45 min [$F(1,25) = 8.7, p < 0.01$], 60 min [$F(1,25) = 7.2, p < 0.05$], and 90 min [$F(1,25) = 8.1, p < 0.01$]. PRL response was also significantly increased in women at 30 min [$F(1,22) = 6.3, p < 0.05$], 45 min [$F(1,22) = 6.3, p < 0.05$], and 60 min [$F(1,22) = 4.6, p < 0.05$], but not at 90 min [$F(1,22) = 1.1$, p = NS]. The difference between TRH-stimulated ΔTSH in female patients versus female controls (Table 1) did not reach statistical significance for ΔTSH_{max} peak (30 min) ($t = 1.9, p = 0.09$) or for AUC for TSH ($t = -2.1, p = 0.06$).

Of the 6 patients who were restudied, 4 (2M, 2F) had deteriorated significantly with an average decline (±SD) in the MMSE of 11 ± 2 [N = 6, $t(5) = -2.6, p < 0.05$].

BIOL PSYCHIATRY 1990;28:144–150

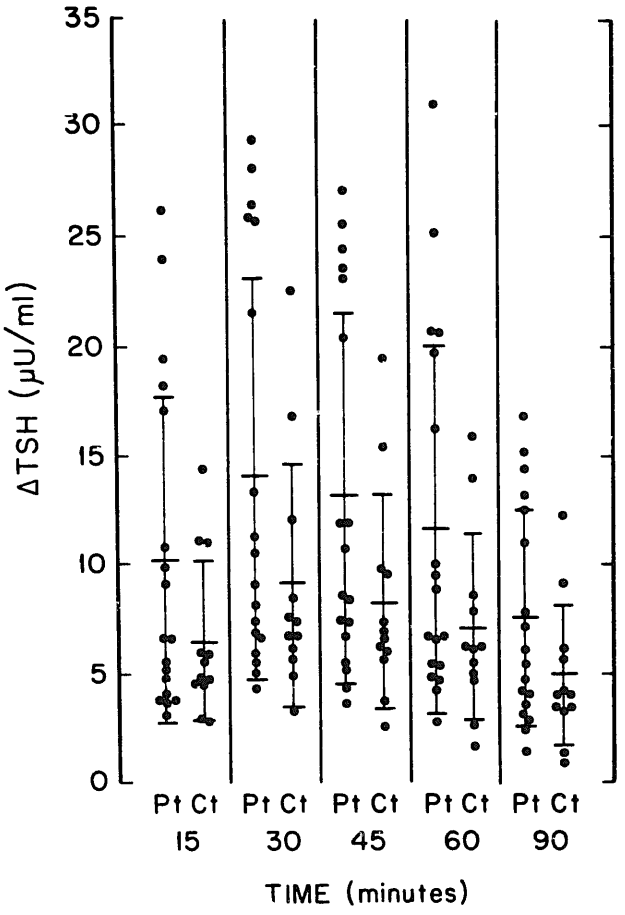

Figure 1. TRH-stimulated ΔTSH for patients (Pt) and controls (Ct) at 15, 30, 45, 60, and 90 min.

The other 2 patients (2M) had remained stable: one patient had a decline of one MMSE point over 24 months, the other had an increase of 3 MMSE points over 30 months. No significant differences were observed between the initial and repeated TRH stimulation tests for either TRH-stimulated ΔTSH or ΔPRL at all time points. Also, the AUCs for TSH and PRL did not differ significantly between these two testing periods.

Discussion

Our findings are in agreement with those studies that did not find significant differences between PDD patients and age-matched controls in TRH-stimulated ΔTSH (El Sobky et al. 1986; Franceschi et al. 1988; Lampe et al. 1988; Peabody et al. 1986) and ΔPRL (Thomas et al. 1987). We did find, however, significantly greater responses in ΔTSH and ΔPRL for women compared with men in both the patient and control groups. Gender differences have been reported among normal euthyroid subjects for TRH-stimulated ΔTSH and ΔPRL. Women tend to have a greater ΔTSH (Ormston et al. 1971), which has not been found to change with age (Snyder and Utiger 1972a). In men, however, an age-associated decline in ΔTSH has been reported (Snyder and Utiger 1972b). These two patterns of TSH responsiveness to TRH in men and women would tend to accentuate gender differences as subjects age. In a recent study on TSH testing in a healthy elderly

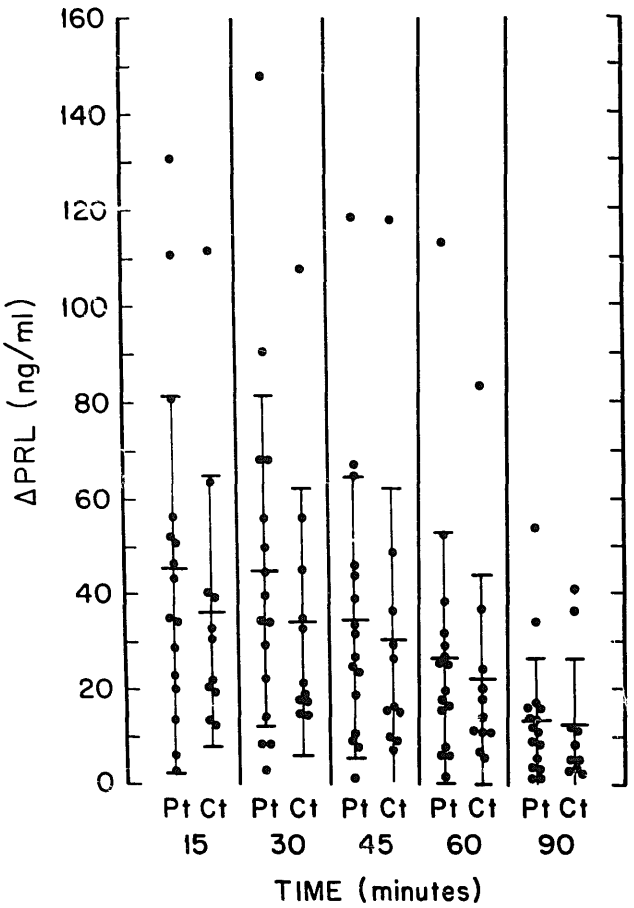

Figure 2. TRH-stimulated ΔPRL for patients (Pt) and controls (Ct) at 15, 30, 45, 60, and 90 min.

Table 1. Gender Differences in TRH-stimulated ΔTSH_{max} and ΔPRL_{max} in Patients with Primary Degenerative Dementia and Age-matched Controls

	Men (M ± SD)	Women (M ± SD)	ANCOVA *F*, *p*
ΔTSH (30 min)			
Patients (n = 18)	9 ± 6	20 ± 9	$F(1.25) = 8.1$
Controls (n = 12)	7 ± 4	11 ± 7	$p < 0.01$
ΔPRL (15 min)			
Patients (n = 16)	30 ± 18	66 ± 44	$F(1.22) = 7.3$
Controls (n = 11)	23 ± 11	53 ± 37	$p < 0.05$
AUC (TSH vs time)			
Patients (n = 18)	609 ± 420	1374 ± 588	$F(1.25) = 8.7$
Controls (n = 12)	497 ± 298	750 ± 391	$p < 0.01$
AUC (PRL vs time)			
Patients (n = 16)	1969 ± 1342	3792 ± 2874	$F(1.21) = 4.3$
Controls (n = 10)	1309 ± 657	3344 ± 2872	$p = 0.05$

M = mean; ΔTSH_{max} = ΔTSH (30 min); ΔPRL_{max} = ΔPRL (15 min); ANCOVA F = main effect of gender with age as covariate; AUC = area under the curve.

population, men showed a significantly diminished TSH response to TRH administration compared with women (Targum et al. 1989).

The PRL response to TRH has been reported to be greater in women than men, especially in young and middle-aged subjects (Jacobs et al. 1973). Among subjects of the same gender, ΔPRL responses were comparable from ages 20–80, although the response in elderly women was somewhat lower than that of the younger groups of women (Jacobs et al. 1973).

It is of interest that 2 PDD patients (MMSE = 28, 21) did not demonstrate cognitive decline when repeated testing was carried out after approximately 2 and 2½ years, respectively. Rates of progression for PDD do vary considerably and it is not uncommon for periods of relative cognitive stability to occur during the early course of the illness (Grady et al. 1988). Nevertheless, it is also known that at best, approximately 10% of patients with a clinical diagnosis of PDD will not meet autopsy or biopsy criteria for a pathological diagnosis of Alzheimer's disease (Riege and Metter 1988). Removing these two cognitively stable patients from the data set did not, however, change the overall results. The statistically significant gender differences were maintained for both ΔTSH and ΔPRL, although ΔPRL at 60 min just missed retaining an alpha level of 0.05 [$F(1,20) = 3.97$, $p = 0.06$] as did the AUC for PRL [$F(1,19) = 3.8$, $p = 0.06$]. Again, no significant differences were observed between patients and controls for TRH-stimulated ΔTSH and ΔPRL at all time points.

Our data suggest that the presence of primary degenerative dementia does not alter gender-associated differences in TSH and PRL responsiveness to TRH stimulation. Some of the previous TRH stimulation studies in Alzheimer's disease failed to show gender differences because either all the subjects were men (Lampe et al. 1988; Peabody et al. 1986) or gender differences were not examined for specifically (Newhouse et al. 1986; Thomas et al. 1987). One study did find a trend toward greater TSH responsiveness to TRH in women patients (Sunderland et al. 1985), but another study found no gender differences at all (El Sobky et al. 1986). In this latter study the timing of the blood collections were 20 min and 60 min after TRH administration. It is unlikely that the timing of blood samples for TSH measurement would account for these negative results as gender differences for TRH-stimulated TSH were found at all time points in our study.

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