

**COGNITIVE CHANGES AND BASAL THYROTROPIN IN TREATED AND  
UNTREATED PATIENTS WITH ALZHEIMER'S DISEASE**

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SUMMARY

We assessed cognitive changes (measured with the Mini-Mental Status Examination questionnaire; MMSE) and baseline thyrotropin (TSH) levels in 17 patients treated with cholinesterase inhibitors (Group A), 16 patients treated with tacrine (Group B), 15 patients treated with various nootropics (Group C) and 53 patients under no systematic treatment (Group D). Only in Group A patients, a relation of yet-unknown pathophysiological significance could be suggested between TSH and the MMSE score after 4-8 months of treatment.

Keywords: Alzheimer's disease, humans, retrospective studies, thyroid function tests

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## INTRODUCTION

Results of epidemiologic studies of thyroid disease as a possible risk factor for Alzheimer's disease (AD) have been conflicting (1-6). However, subtle changes in thyroid function have been reported in patients with AD, including an abnormal thyrotropin (TSH) response to thyrotropin-releasing hormone (7). Furthermore, thyroid function tests may be influenced by medications (cholinesterase inhibitors) given to hasten the progress of AD (8). Since of all thyroid function parameters the measurement of TSH only is considered to be an adequate screening test, the aim of the present study was to assess cognitive changes (measured with the Mini-Mental Status Examination questionnaire; MMSE) and baseline TSH levels in treated vis-à-vis untreated outpatients with AD.

## SUBJECTS AND METHODS

The following groups of patients were studied over a period spanning more than 15 years: Group A with 17 patients (2 men, 15 women; mean age $\pm$ SD: 70.1 $\pm$ 9.7 years) under cholinesterase inhibitors (donepezil or rivastigmine) treatment. Group B with 16 patients (6 men, 10 women; mean age $\pm$ SD: 69.1 $\pm$ 7.9 years) under tacrine treatment. Group C with 15 patients (7 men, 8 women; mean age $\pm$ SD: 69.9 $\pm$ 9.1 years) treated with various nootropics (like piracetam). Group D with 53 patients (13 men, 40 women; mean age $\pm$ SD: 70.3 $\pm$ 7.3 years) under no systematic treatment. It is important to point that groups B, C and D included patients that were followed more than 10 years ago, before the advent of cholinesterase inhibitors therapy (thus there is no issue of having held back necessary therapy from patients). All patients had AD according to the NINCDS-ADRDA criteria (9), were free from known thyroid disease and did not receive any thyroid disease-altering medication. Assessment included administration of the MMSE at the first office visit and after 4-8 months, since patients treated with cholinesterase inhibitors (the current medication of choice for AD) show cognitive improvement within approximately the first 6 months of administration; a gradual decline follows (10). Laboratory evaluation of TSH was done at the initial visit with a third generation commercial chemiluminescence assay (normal laboratory range: 0.4-4.2 microIU/mL). Statistical analysis of differences in MMSE and TSH among the various groups was done with analysis of variance (ANOVA) and post-hoc Student-Newman-Keuls testing for pairwise comparisons. Within each group log TSH versus change in MMSE was assessed with linear regression. Statistical significance was set at P = 0.05.

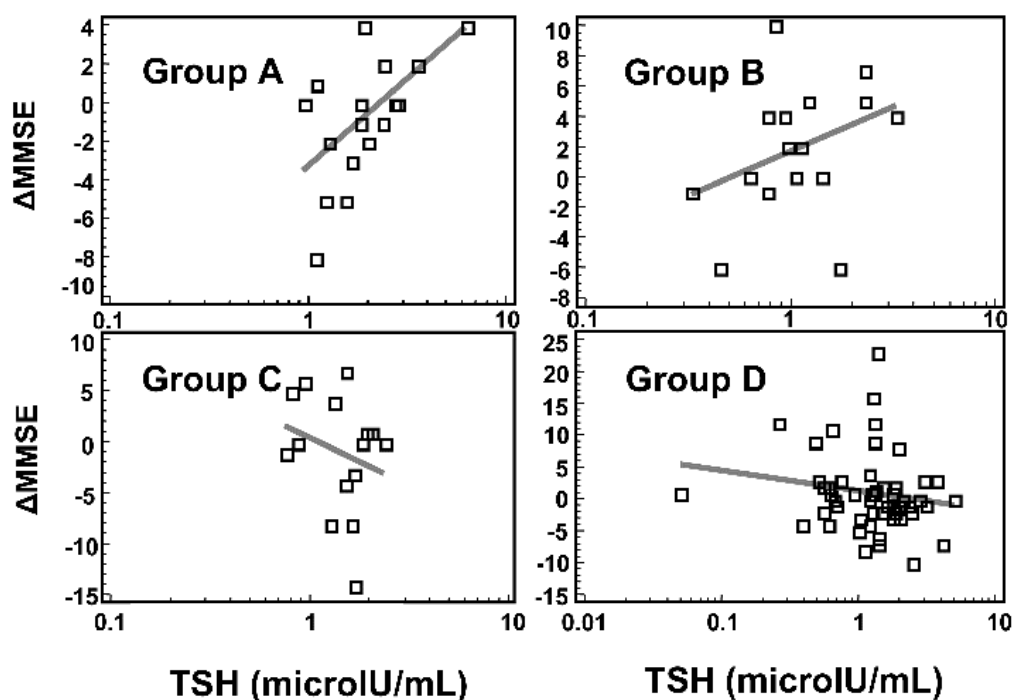
## RESULTS

TSH levels were within normal limits for almost all subjects. ANOVA results (F-ratio = 7.046, P = 0.009) and Student-Newman-Keuls test for pairwise comparisons showed that the patients who were treated with cholinesterase inhibitors had higher baseline TSH (Table 1). Only in group A, linear regression of  $\Delta$ MMSE against log TSH reached statistical significance (Table 1 & Figure 1)

TABLE 1: Descriptive statistics for each studied group:

	Group A	Group B	Group C	Group D
TSH (microIU/mL) (mean±SD)	2.12±1.26	1.26±0.79	1.43±0.49	1.59±0.96
MMSE 1 (t = 0) (mean±SD)	14.2±4.4	16.4±6.6	13.0±7.3	16.4±5.4
MMSE 2 (t = +4 to +8 months) (mean±SD)	15.1±4.9	14.0±4.4	14.5±7.3	15.8±5.8
ΔMMSE (MMSE 1 – MMSE 2) (mean±SD)	0.8±3.2	1.8±4.3	-0.9±5.8	0.9±5.9
Linear regression of ΔMMSE against log TSH (r, 95% confidence interval)	+0.59 (+0.16 to +0.84)	+0.36 (-0.17 to +0.73)	r = -0.25 (-0.68 to +0.29)	r = -0.18 (-0.43 to +0.09)
P of linear regression	0.01	0.17	0.36	0.21

FIGURE 1: Linear regression (ΔMMSE against log TSH) for the groups studied. Please note that the axes' values are not identical for all graphs.



## DISCUSSION

In this small-scale retrospective study, in patients treated with cholinesterase inhibitors, a relation of yet-unknown pathophysiological significance could be suggested between TSH and the MMSE score. This finding may not be surprising, taking into account the observation that cognition is linked to thyroid function (11, 12). Furthermore, in the light of newer data (13-15) the normal range of TSH may be narrower than what was previously considered (with an upper cut-off normal level of 2.00 to 3.50 microIU/mL). As a matter of fact, a TSH value higher than 3.00 microIU/mL is considered by some researchers as a sign of subclinical hypothyroidism and an indication for thyroxine replacement therapy (16) [this issue is still controversial, not all experts agree with these changes (17)]. Thus, it appears that low (but within what is considered to be broadly normal) TSH is associated with less deterioration in the MMSE. This study has limitations that should be mentioned. First, that among the patients that were studied the ones treated with cholinesterase inhibitors were few (17/101 total patients). Second, that the thyroid function laboratory work-up was limited to the measurement of TSH, which is considered to be adequate for screening. Nevertheless, other -- eventual -- associations between parameters of cognitive function and thyroid hormones *per se* [triiodothyronine in particular (8)] were not included (more assays would have necessitated more patients to reach statistically meaningful results). In conclusion, to assess whether TSH can be of utility as a surrogate measure to predict cholinesterase inhibitors' effectiveness in AD further studies are warranted.

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