CHANGES OF EVENT RELATED POTENTIAL AND COGNITIVE PROCESSES IN PATIENTS WITH SUBCLINICAL HYPOTHYROIDISM AFTER THYROXINE TREATMENT

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Objective. Recently, it has been repeatedly shown that patients with subclinical hypothyroidism (SH) formerly considered as completely symptom free, may have numerous minimal, often non-specific subjective complaints, and that in those patients it is possible to prove many subtle but objective deviations. We decided to quantify whether there are event related potential (ERP) deviations as electrophysiological markers of cognitive activity in patients with SH and whether ERP could be influenced by thyroxine treatment leading to normalization of TSH level in serum.

Subjects and design. Event related potential (ERP) was examined in thirty one patients (mean age 52±12.5 years) with SH and without any other endocrine or metabolic diseases and in 29 subjects of the control group. From 31 patients 20 women (mean age 61.8±6.8 years) were selected and divided into a group of 10 women treated six months with L-thyroxine until the normalization of TSH and remaining 10 women receiving placebo. ERP examination was repeated and all such patients also underwent neuropsychological examination consisting of the Wechsler Memory Scale and the MMPI/100 (Minnesota Multiphasic Personality Inventory). The interval between the diagnosis of SH and final evaluation of treatment was 16 months .

Results. In SH thyroxine treated patients the average P3 wave latency was 374 ms (SD 40.6) , while in placebo group it was 340 ms (SD 32.3. $P<0.01$). In addition, the treatment with thyroxine normalized the TSH level resulted in a decrease of P3 wave latency from 374±36.3 ms to 343±16.3 ms ($P<0.01$). However, in the placebo group such changes were not observed, the latency of P3 being 387±24.3 ms at the beginning and 379±36.5 ms at the end of observation period. No significant correlations between P3 wave latency and thyroid parameters were found. In thyroxine treated group a significant improvement in verbal memory ($P<0.01$), visual memory ($P<0.01$) and total memory scores ($P<0.01$) was found, while no changes in these parameters were observed in the placebo group. No significant differences were found in the MMPI test evaluation.

Conclusions. SH patients had significantly longer P3 wave latency in ERP examination as compared to healthy individuals which gives evidence for impaired cognitive functions in SH patients. In these patients the normalization of TSH level by thyroxine treatment resulted also in the normalization of P3 wave latency. In addition, also verbal, visual and total memory scores improved significantly with the TSH normalization.

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Key words: Subclinical hypothyroidism – Thyroxine treatemnt – Event related potential –Memory scores

Isolated TSH increase in patients completely free of any symptoms of thyroid disorders and with normal total and free thyroid hormone levels is quite a frequent phenomenon which affects 3 to 7 percent of middle aged population. The frequency of such cases in the population over 60 years of age, especially in women, may be as high as 17 percent (Arem et al. 1996). This status is generally considered as subclinical hypothyroidism, but we can meet also with terms like preclinical or early hypothyroidism, decreased thyroid reserve, compensated hypothyroidism, latent hypothyroidism, minimal thyroid failure or recently also with minimal symptomatic hypothyroidism (Ayala et al. 1997). This last term seems to give the truest picture of the problem.

Recently, it has been shown that the patients formerly considered as completely symptom free, may have plenty of minimal, often non-specific subjective complaints, and that in those patients it is possible to prove many subtle but objective deviations compared to euthyroid individuals. It has been also shown that there is a continuous transition from eu- to hypothyroidism and thus, when evaluating the patient, both the degree and duration of thyroid impairment should be considered (Cooper 1998). The neuropsychological problems in clinically apparent hypothyroidism have been well known and documented (Whybrow 1969).

Considering that the patients with isolated increased TSH level and thus also with subclinical hypothyroidism often complain of similar, but clinically very mild symptoms, we decided to quantify whether there are event related potential deviations (ERP) as electrophysiological markers of cognitive activity. As a second step, we tried to evaluate the influence of the thyroid status normalization on the ERP values during the thyroxine therapy.

Subjects and Methods

Laboratory methods. The levels of thyrotropin (TSH), free thyroxine and triiodothyronine (FT4 and FT3) and anti-thyroperoxidase antibodies (anti-TPO) were estimated with commercial kits purchased from BRAHMS Diagnostica (Berlin, Germany), the intra-assay variation for all kits being 1.5-5.0 % and inter-assay variation 3.5-6.5 %.

Subjects. Thirty one patients (average age of 52±12.5 years, including 28 women) with subclinical hypothyroidism (SH) and negative history of neurological, psychiatric, endocrine and metabolic diseases were examined. They did not have any long-term medication history and did not take any medication during the observation period.

The average interval between the first diagnosis of SH and ERP examination was 16±6.2 months. As the SH criterion, we considered repeatedly found TSH level >6.0 mU/l.

In all patients the basic diagnosis was chronic autoimmune.thyreoiditis which in 22 cases displayed the atrophic variant and in 9 cases the goitrous variant. The average initial TSH values were in hypothyroid range (8.8±3.7 mU/l), while these of FT_4 were predominantly in the lower normal range (average of 13.7±2.3 pmol/l) and these of FT_3 were within the normal range (average 6.8±1.1 pmol/l). All patients had positive anti-TPO (average 1024±276 U/ml).

Twenty nine symptom free subjects with average age of 63±9 years (for definition see above) including 23 women served as the control group. There were no significant differencies found in the lipoprotein spectrum between the patients and controls.

For the examination of thyroxine treatment effect on ERP in SH patients, we further selected from the patients previously examined a group of 20 women (average age of 61.8±6.8 years) with SH (as defined above) who showed a good compliance. They were further divided into a group of 10 women treated with thyroxine until the normalization of TSH levels for 6 months and other 10 women with placebo treatment for 6 months. This protocol (grant IGA3544-3) was approved by the hospital Central Ethical Committee and all participating subjects gave their written informed consent..

The cognitive event related potentials were generated using the discriminative task type "odd-ball" by binaurial stimulation with earphone tones in 50 ms length, 75 dB SPL intensity and interstimulation interval 1.4 s. The examined persons were instructed to add up in their mind the target 2 kHz frequency tones occuring incidentally (P=0.2) in series of more often occuring (P=0.8) indifferent 1 kHz frequency tones which should have been neglected. The resulting ERP curves were obtained by the average of the individual records after achieving minimally 20 target stimulus responses. The examination was performed twice to check the reproducibility. The evoked responses were

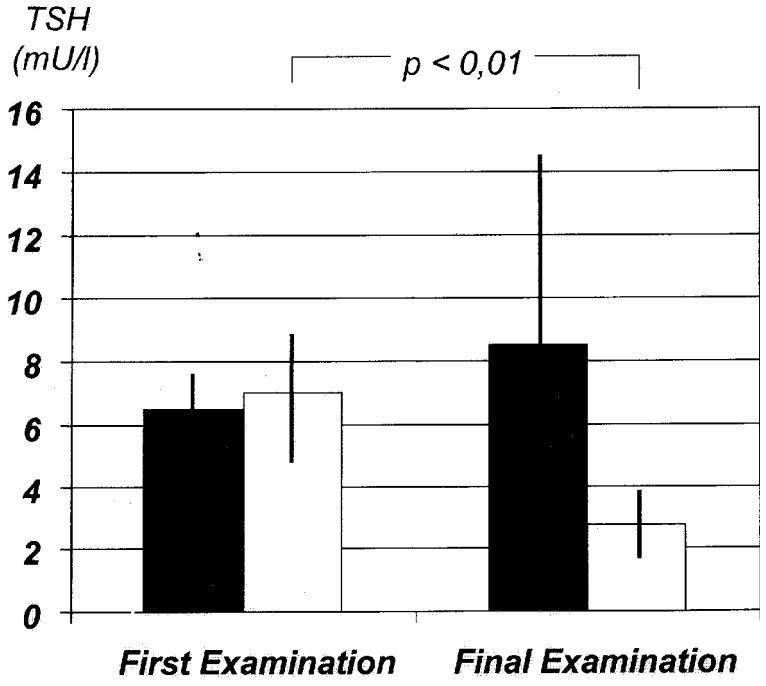

Fig. 1 Differences in TSH values in SH placebo treated and L-thyroxine treated group at the beginning of the study and after six months. Black columns – placebo treated group; white columns – thyroxine treated group.

registered from Cz-M 1.2 lead (system 10-20). The associated reference electrodes M1 and M2 were situated above the left and right mastoid process. The individual ERP components, i.e. N1, P2 after non-target and N1, N2, P3 after the target stimulus were identified in the record by the standard procedure.

Neuropsychological examination was conducted in all SH patients by a clinical psychologist and consisted of the Wechsler Memory Scale (revised version) from the cognitive point of view and the MMPI/100 (Minnesota Multiphasic Personality Inventory) from the personality point of view.

Statistical evaluation. For the comparison of the examined SH patients with controls we used an F-test and the Student´s double choice t-test with unequal scatter. For the comparison of thyroxine treated patient and control group, considering the same number of subjects in each group, we used a pair t-test to evaluate the results.

Results

It was found that the average P3 latency in SH patients was significantly higher (374±40.6 ms, mean±S.D.) than in control subjects (340±32.3 ms; $P<0.01$). However, in six SH patients the P3 waves reached the pathological values (i.e. more than the mean plus 2 S.D.). The other evaluated parameters (N1, P2, N2 in response to target and non-target stimulus) did not show any significant differences between both groups. The mean TSH value in the SH group was 8.8±2.7 mU/l (mean±S.D.).

Figure 1 shows that in thyroxine treated SH patients the initial TSH levels (7.1±2.1 mU/l) decreased significantly to 2.8±1.4 mU/l ($P<0.01$) after 6 months of treatment. In contrast, no significant changes were found between the initial TSH levels (6.6±1.00 mU/l) and these at the end of the observation period (8.4±5.8 mU/l) in placebo treated group. At the same time, in the above thyroxine treated SH patients the P3 wave latency decreased significantly from the initial value of 374±36.3 ms to 343±16.3 ms after 6 months of treatment ($P<0.01$), while in placebo treated groups no significant difference has been found , the initial value being 387±24.3 ms and the final one 379±36.5 ms (Fig. 2).

In thyroxine treated group significant improvements between the initial and post treatment scores

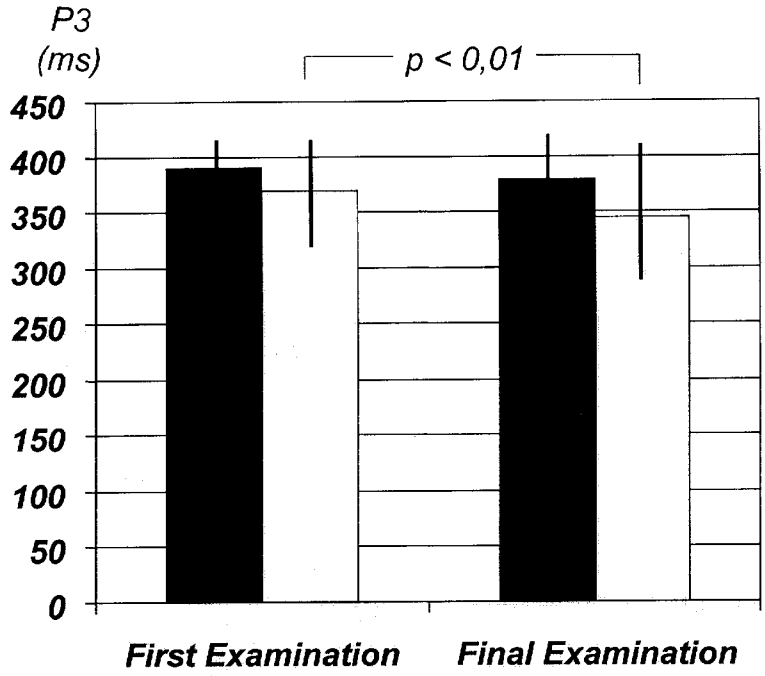

Fig. 2 L-thyroxine treatment of SH patients results in significant P3 value shortening. Black columns – placebo treated group; white columns – thyroxine treated group.

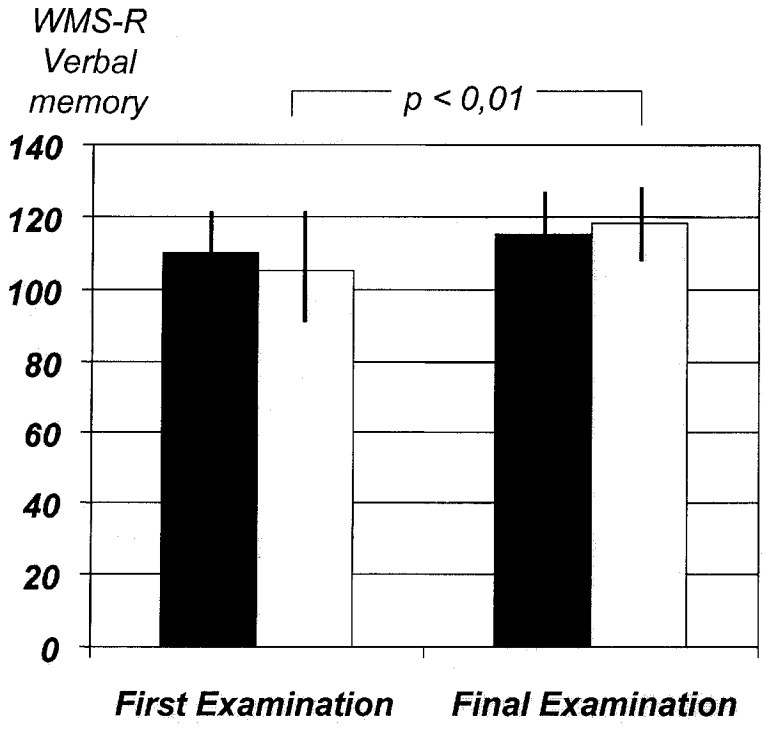

Fig. 3 Verbal memory improves significantly in SH patients during L-thyroxine treatment. Black columns – placebo treated group; white columns – thyroxine treated group.

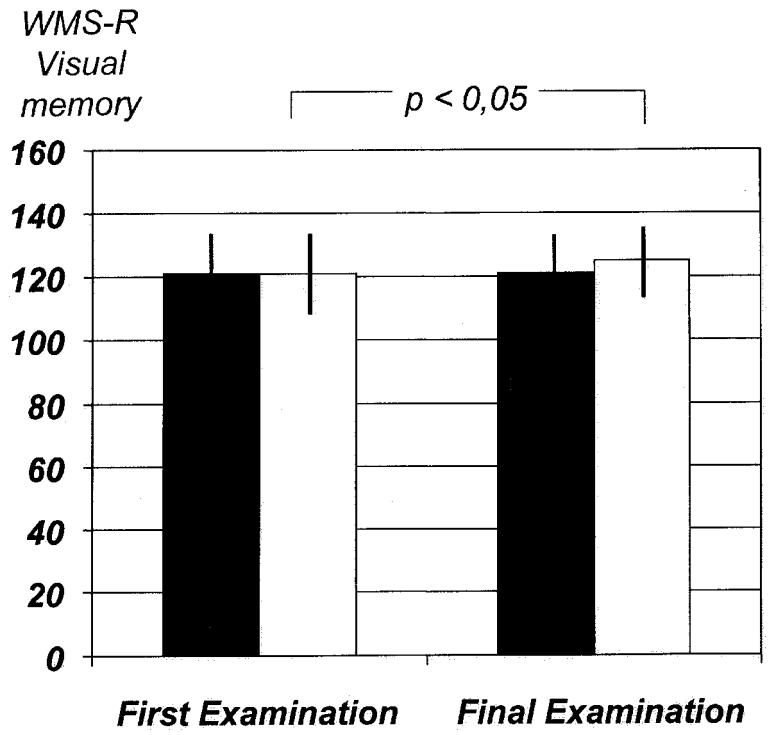

Fig. 4 Visual memory improvement in SH patients after thyroxine treatment. Black columns – placebo treated group; white columns – thyroxine treated group.

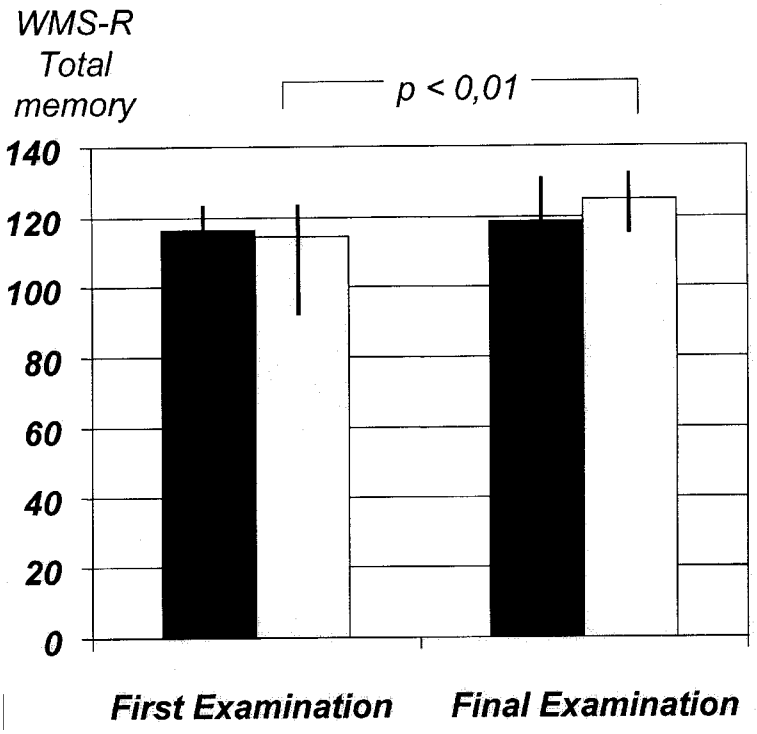

Fig. 5 Also total memory score improves significantly during the six month L-thyroxine treatment of SH patients. Black columns – placebo treated group; white columns – thyroxine treated group.

were found in the verbal memory ($P<0.01$; Fig. 3), visual memory ($P<0.05$; Fig. 4) and total memory ($P<0.01$; Fig. 5), while no changes were observed in the placebo treated group (see the respective Figs. 3, 4 and 5). No significant differences or changes were found also in the MMPI test evaluation.

Discussion

In patients with clinically clearly manifested hypothyroidism numerous neurological, neuromuscular, psychological and cognitive abnormalities have been described (Whybrow 1969). However, in some psychiatric disorders also the subclinical hypothyroidism has been found more often (Howland 1993). Some authors have followed the frequency of psychiatric disorders also in SH, but they mainly examined the psychological and cognitive disorders with the aid of several tests (Monzani 1993). However, such tests are only a subjective method of examination, are time consuming and hardly repeatable in more frequent intervals. This is why we decided to use for examination the ERP method as a rapid, repeatable and mainly objective method (Nishitani et al. 1968).

So far, there are only few reports on this topic in the literature. Thus, Osterweil et al. (1992) examined several patients with different degrees of hypothyroidism using psychological as well as electro-physiological methods. They proved a series of deviations in psychological tests targeted at cognitive function, but they did not find any ERP differencies, mainly any P3 wave latency change. On the contrary, in our SH patients we found a significant P3 wave latency enlargement compared to control individuals. However, it should be underlined that our patients had increased TSH levels for a long time with low normal FT4 values, while Osterweil et al. (1992) examined the newly diagnosed patients and did not find any psychological and cognitive disorders in the subgroup of patients with short-term but manifested hypothyroidism, e.g. after strumectomy. The decisive factor for the development of psychological cognitive disorders seems to be the duration of hypothyroidism rather than its degree as evaluated by TSH level.

As far as neurological methods are concerned, the patients with SH have been examined also by the distal motor latency measurement, the neural conduction rate, muscular activation potentials and F response in medial and peroneal nerve (Ozata et al. 1995). The sensomotoric nerves examination was performed on the sural and medial nerve and the patients underwent the ERP examination as well. The time interval between the diagnosis estimation and the examination date was again only 2.5 months on the average. These authors found no significant deviations as compared to a control group. We assume that the possible explanation is again too short time of SH duration.

The inconsistent findings concerning the peripheral motor nerve conduction were published by other authors as well. Thus, some of them did not find any changes (Misiunas et al. 1995), while some others (Monzani et al. 1997) found not only EMG changes in 8 out of 11 patients with SH, but also significant changes in muscle metabolism, especially in the load condition, which correlated positively with the SH duration. Recently, the stapedial reflex disorder, which is one of the neuromuscular affection markers, has been described in SH patients (Goulis et al. 1998).

The question of explaining the reversibility of the observed changes during the thyroxine therapy appears rather more complicated. Thus, in the above mentioned publications the changes in the observed parameters were not always presented, the amelioration correlating with the TSH level normalization being clearly reported only in the case of stapedial reflex examination (Goulis et al. 1998). In our patients we scrutinized the P3 wave latency normalization after the TSH normalization in all examined persons and the difference was significant at the 1 percent level of significance. On the contrary, in the placebo group there was no tendency to P3 wave latency changes registered. From this point of view it is interesting that recently the thyroxine therapy was proved to contribute to significant neurotransmitter level changes in the cerebrospinal fluid (Sjoeberg et al. 1998). According to these authors there is an interrelation between the thyroid function and the phenylalanine and tyrosine levels in the cerebrospinal fluid.

All the described findings support the use of thyroid hormone in the treatment of depressive disorders which has been so far based rather on empirical basis only (Howland 1993; Joffe 1998; Prange 1996;

Whybrow 1994). Nevertheless, for instance, even in respect to the substitution treatment of hypothyroidism, the positive influence of low triiodothyronine doses on the subjective condition of the patient has been recently called into a question (Bunevicius et al. 1999). Moreover, the lymphocytic thyroiditis alone, which affected all our patients, can cause the encephalopathy with mild cognitive function affection (Kothbaumargreiter et al. 1996). The direct influence of the autoimmune thyropathies on the central nervous system is mentioned also by other authors (Forchetti et al. 1997; Ganguli et al. 1996). Our results confirm the normalization of the subclinical cognitive disorders in patients with SH after TSH values normalization.

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