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Short-term hypothyroidism in thyroid cancer patients and cognitive-motor performance relevant for driving

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Driving ability

Summary
Context: In patients with differentiated thyroid carcinoma (DTC) who, after thyroidectomy, are to receive radioiodine therapy or diagnostics, a strong TSH stimulus is necessary. Traditionally, this is induced by thyroid hormone withdrawal (THW) over a period of 4—5 weeks; alternatively thyroid hormone replacement therapy is continued and recombinant human thyrotropin (rhTSH) is administered. During the hypothyroid state due to THW, patients often report mood disturbances and physical complaints but also an impairment of performance during attention demanding tasks.
Objective: Based on physiological, self-report and performance test data collected from various studies, we proposed the hypothesis that thyroidectomized DTC patients perform significantly worse in cognitive-motor functions that are relevant for driving when in the THW-induced hypothyroid state compared to when thyroid hormone replacement therapy is continued and rhTSH is administered.
Methods: We compared 41 DTC patients (age 42.3 (9.4) years; 80.5% female) after 4 weeks THW with 41 DTC patients after the application of rhTSH, pairwise matched according to age, gender and educational level, with respect to performance in 4 core tests of the Act-React-Testsystem ART-90, a validated test battery for examining fitness to drive.
Results: Contrary to our expectations, no statistically relevant impairment of performance could be confirmed in the THW group in comparison to the rhTSH group for any variable (at adjusted α). At most there is a tendency in the THW group for slowed reaction times in simple-choice reaction tasks; the (standardized) difference to the rhTSH group is however small ($d' = 0.31$). Furthermore, large effects due to THW, as they are suggested by several studies, could be excluded.

1. Introduction

In patients with differentiated thyroid carcinoma (DTC) who, after thyroidectomy, are to receive radioiodine therapy (ablation of remnants or therapy of recurrences or metastases) or follow-up diagnostics (measurement of stimulated thyroglobulin and/or radioiodine whole-body scintigraphy) an

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elevated concentration of thyroid stimulating hormone (TSH) is necessary.

Traditionally, TSH elevation in DTC patients is achieved by interruption of thyroid hormone replacement therapy, i.e. by thyroid hormone withdrawal (THW) for 4—5 weeks (endogenous TSH stimulation). Alternatively recombinant human TSH (rhTSH) can be administered (exogenous TSH stimulation), which has been approved since several years for the radioiodine ablation of remnants and for diagnostic purposes during follow-up, but not for the radioiodine therapy of recurrences and metastases. At exogenous TSH stimulation, patients remain on thyroid hormone replacement therapy and thus are not subjected to the psychological strains of the hypothyroid state.

Clinical experience and systematic surveys have shown, that during THW patients suffer from a variety of disturbances, in particular toward the end of the period. Alongside typical somatic symptoms, they often report: listlessness, anxious-depressive upset, impairment of attention and concentration, deficits of memory, cognitive and motor slowing (Denicoff et al., 1990; Burmeister et al., 2001; Botella-Carretero et al., 2003; Constant et al., 2006), and, in total, a reduction of quality of life (Dow et al., 1997; Botella-Carretero et al., 2003; Tagay et al., 2005; Schroeder et al., 2006).

In the current study we ask, whether in DTC patients THW induced hypothyroidism causes impairments of cognitive-motor functions that affect the ability to drive. We thus focus on a functional area, that can be described by a list of performance areas or requirements pursuant to the German Driver's Licence Act (FeV), Appendix 5 (Bundesministerium für Justiz, 2010): visuo-spatial perception/orientation, attention, concentration, speed and reliability of reaction, stress tolerance. We address our question by examining patients who undergo radioiodine whole-body scintigraphy.

There are several results, collected from studies on different aspects of functioning, which support the assumption that THW causes impairments in the areas mentioned above: (a) physiological, (b) self-report, and (c) performance test data.

(a) Using positron emission tomography (PET) Constant et al. (2001) demonstrated in DTC patients under THW a generalized decrease of regional cerebral blood flow and of cerebral glucose metabolism, as compared to the state under thyroid hormone replacement therapy.

In a study by Münte et al. (2004) visual-evoked potentials were recorded, while patients performed visual search tasks. A comparison of ERPs (electrode site: Pz) on thyroid hormone replacement therapy and following THW showed a reduction of the standard-target amplitude difference and a delay of the difference onset in the hypothyroid session, namely in the serial search version, during which the detection of the target stimulus requires an item by item scanning of the visual array. According to the authors this result is a clear indication of a reduction of attentional resources as needed for everyday tasks such as driving a car.

(b) From studies covering a broader range of topics we report a number of findings that seem relevant in this context:

In a study conducted by Botella-Carretero et al. (2003) scores for self-rated attention following THW were lower than those on thyroid hormone replacement and than those of healthy controls of similar age and cultural background. Denicoff et al. (1990) and Dow et al. (1997) reported significantly lower self-rating scores for concentration in the hypothyroid state than on replacement therapy. In a study by Burmeister et al. (2001) patients were asked how much difficulty they had to stay alert and maintain concentration (ignoring distracting stimuli); the scores after THW were significantly higher than those under thyroid hormone replacement. In a previous study of our working group (Tagay et al., 2005) patients in the hypothyroid state following THW indicated significantly more frequently that they felt slower in their movements, than patients did who were on replacement therapy.

(c) Our review of the literature revealed two studies with DTC patients, in which (in addition to other procedures) performance tests were used that measured abilities of substantial relevance to our research topic: First, in a study by Constant et al. (2006), (23) DTC patients were examined while on levothyroxine treatment and after 4 weeks of THW, using the subtest 'Phasic Alertness' from the Testbattery for Attentional Performance (TAP). Alertness was measured based on the time to respond to a target stimulus with and without a warning signal. The reaction times were significantly longer when patients were in the hypothyroid state. Second, in the study by Münte et al. (2004) mentioned above, the patients ($n = 15$) were examined after 4 weeks of THW (t1) and 2—3 months after resuming the replacement therapy (t2): (a) The d2 Test of Attention was administered, a procedure that was originally designed to examine the fitness to drive and to work safely at specific workplaces. At t1 the test subjects displayed significantly worse results than at t2. (b) The patients performed parallel and serial visual search tasks. The reaction times were increased at t1 in both types of task; in the serial version the effect was more than twice as large as in the parallel version (8-item array). The hit rate was reduced at t1 only in the serial version (relative to t2). This shows that particularly during the cognitively more challenging task thyroid hormone withdrawal led to a decrease of performance.

Summarizing these results (a—c), we think there is sufficient empirical evidence to propose a directional hypothesis: Thyroidectomized DTC patients undergoing radioiodine diagnostics exhibit expressly worse performance in the target areas when they are in a THW induced hypothyroid state, relative to when thyroid hormone replacement therapy is continued and rhTSH is administered.

2. Methods

2.1. Study design

We chose a matched-pairs design, (a) to take advantage of the fact that in a comparison of correlated groups the error variance is less than in the comparison of independent groups, and (b) to avoid material-specific and/or situation-specific repeat effects as well as possibly selective drop-out effects as could be expected in a repeated measurement design. Matching was undertaken according to age, gender and educational level, as these are factors that affect the performance functions in which we are interested. The grid of matching variable combinations was based on the data of the patients in the THW group as a potential target group for