Psychoneuroendocrinology (2004) **29**, 917–924

PNEC

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Relationship between mood and TSH response to TRH stimulation in bipolar affective disorder

J.K. Larsen[c,*], J. Faber[b], E.M. Christensen[a], B.B. Bendsen[a], K. Solstad[a], A. Gjerris[c], K. Siersbæk-Nielsen[b]

[a]*Department of Psychiatry A, H:S Frederiksberg Hospital, Ndr. Fasanvej 57, DK-2000 Frederiksberg, Denmark*
[b]*Department of Endocrinology E, H:S Frederiksberg Hospital, Ndr. Fasanvej 57, DK-2000 Frederiksberg, Denmark*
[c]*Gentofte Psychiatric Centre, Niels Andersensvej 65, DK-2900 Hellerup, Denmark*

Received 4 November 2002; received in revised form 19 August 2003; accepted 26 August 2003

KEYWORDS
Bipolar affective disorder; Hamilton Depression Rating Scale; Bech-Rafaelsen Mania Scale; Thyroid stimulating hormone; TSH releasing hormone; TRH test

Summary Moderate to severe depression and mania are associated with a reduced thyroid stimulating hormone (TSH) response to TSH releasing hormone (TRH). Continued reduction of this response after clinical recovery seems indicative of early relapse. The aim of the present study was to test the relationship between mild changes in mood and the TSH response to TRH stimulation in patients with bipolar affective disorder. Nineteen outpatients with bipolar affective disorder were followed prospectively for three years. Every third month, mood symptoms were rated using the 17-item Hamilton Depression Rating Scale (HAMD-17) and the Bech-Rafaelsen Mania Scale (BRMS). A TRH test was performed in connection with each rating session (IV injection of 200 μg TRH), and serum TSH was measured at 0, 20, and 60 min. The maximum TSH response (D-max TSH) and the temporal change in D-max TSH between succeeding rating sessions (DD-max TSH) were determined. Psychometric rating and TRH data were obtained for a total of 198 examinations. The temporal change in mood symptom rating score was negatively correlated with the temporal change in D-max TSH, thus suggesting that increasing severity of mood symptoms was related to a reduced TSH response to TRH stimulation. The temporal change in TSH response to TRH stimulation correlated with the actual score on an overall index of symptom severity. In conclusion, milder fluctuations in mood in bipolar affective disorder seem to correlate with the TSH response to TRH stimulation: Increasing severity of mood symptoms seems to be associated with reduced TSH response.

1. Introduction

Scientific studies over the past 30 years have demonstrated changes in the hypothalamic–pituitary–thyroid axis (HPT axis) in patients with

*Corresponding author. Tel.: +45-3977-3654; fax: +45-3977-7600.
E-mail address: jela@gentoftehosp.kbhamt.dk (J.K. Larsen).

0306-4530/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.psyneuen.2003.08.004

depression and to some extent also in patients with other psychiatric diseases (Kirkegaard and Faber, 1998). The lack of standardized patient classification hinders meaningful comparison of the studies, however. The most consistent findings derive from patients with major depression, in whom serum levels of thyroid stimulating hormone (TSH) seem to be reduced, although still within the normal range (Maes et al., 1989, 1993). TSH response to TSH releasing hormone (TRH) stimulation is also reduced in patients with major depression (Kirkegaard, 1981). Moreover, their serum T4 levels—both total and non-protein-bound (free)—are consistently normal or increased, whereas the serum T3 levels are normal (Kirkegaard, 1981; Baumgartner et al., 1988). As evaluated by tracer studies, daily production of T4 was 30% above normal in depressed patients, while T3 production was normal (Kirkegaard et al., 1990). In the latter patients the serum TSH level was normal, not reduced. The possibility must be taken into account that the TRH test could be influenced by lithium through intrathyroidal inhibition of thyroid hormone release (Kirkegaard, 1981). Whether this response is of clinical significance has not been prospectively studied in lithium-treated patients with bipolar affective disorder. Taken together, these findings suggest some degree of centrally mediated hyperactivity of the HPT axis during depression.

Depressed patients treated with ECT frequently relapse (i.e. from the same episode) into depression early following treatment. Moreover, it has repeatedly been demonstrated that the initially reduced TSH response to TRH stimulation has not normalized in patients who rapidly relapse into depression (Kvist and Kirkegaard, 1980; Kirkegaard, 1981; Krog-Meyer et al., 1984). The lack of temporal change in TSH response seems indicative of early relapse, suggesting a lack of biochemical recovery despite clinical recovery. It is unclear whether these changes in the HPT axis are a consequence of depression or precede it.

Patients with bipolar affective disorder have frequent relapses/recurrences, but may also experience milder changes in mood. Whether the latter changes in mood are also accompanied by changes in the HPT axis is unknown. The present study therefore investigated whether there is a relationship between mild changes in mood and the TSH response to TRH stimulation in patients with bipolar affective disorder.

2. Methods

2.1. Subjects

The study population consisted of adults aged 18–75 years. A group of patients diagnosed with bipolar manic-depressive disorder according to ICD-8 was identified from the records of the Department of Psychiatry, Frederiksberg Hospital for the period 1990–1993. Patients who could be reclassified as having bipolar affective disorder according to DSM-III-R codes No. 296.4, 296.5 and 296.6 (American Psychiatric Association, 1987) were eligible for inclusion in the study. Reclassification of the patients was undertaken by one of the investigators (EMC) and confirmed by two others (AG & JKL).

Only patients known to have experienced three or more episodes of bipolar affective disorder requiring hospitalization were included. These episodes had to include at least one episode of depression and one of mania, and the last episode had to have occurred not more than one year prior to inclusion. Thyroid function as evaluated by TSH, T4 and T3 levels was normal in all the patients. The exclusion criteria applied were: Rapid cycling disorder (four or more episodes within a one-year period), endocrine diseases other than well-regulated diabetes mellitus, cannabis and drug abuse, primary alcohol abuse, serious CNS disorders, e.g. CNS infections, brain cancer and epilepsy.

Nineteen patients, 11 women and eight men, mean age 57 years (range 37–75 years) agreed to participate in the study. All the participants were provided with verbal and written information and all gave written informed consent. The study was approved by the local ethical committee and conducted in accordance with the Second Declaration of Helsinki. The patients were followed prospectively for three years.

2.2. Psychometric data

The patients were examined at inclusion and at three-month intervals throughout the study. At each examination the patients were rated using the 17-item Hamilton Depression Rating Scale (HAMD-17) (Hamilton, 1960) and the Bech-Rafaelsen Mania Scale (BRMS) (Bech et al., 1978). Relapse/recurrence was defined as readmission to hospital and/or a HAMD-17 score exceeding 12 (depressive episode) and/or a BRMS score exceeding 10 (manic episode). Mixed state was defined as a combined score on both scales exceeding 12. The change in depression (HAMD-17) rating from one rating session to the next was designated