Electromyographic evaluation of blink reflex as a tool for early diagnosis of neurological dysfunction in patients of hypothyroidism

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ABSTRACT
Background: Neurological dysfunction is an important consequence of hypothyroidism. Some of the neurologic manifestations of hypothyroidism include somnolence, lethargy, impaired memory and concentration, depression and entrapment neuropathy. Rarer but reversible neurological manifestations include cerebellar ataxia, psychosis, dementia and myxedema coma. Purpose: The aim of the present study was to evaluate the usefulness of the blink reflex as a method for obtaining an early diagnosis of central nervous system dysfunction in hypothyroid patients who do not have signs or symptoms of nervous system dysfunction. Methods: Forty-eight patients with mean age 40 (± 11), with newly diagnosed primary hypothyroidism and 20 healthy control subjects were included in the study. The patients were divided into subclinical and overt hypothyroidism. Patients with normal T3/T4 with elevated TSH were considered subclinical hypothyroids. For blink reflex testing, subjects lay supine on a bed in a warm room with eyes gently closed. Recordings were performed with an EMG machine (Nihon Kohdeni’Neuropack), with a filter setting of 20 Hz to 10 kHz, using an analysis time of 50 ms. Recordings were performed with surface recording electrodes (Dantec 13K60, Copenhagen, Denmark). Results: Second ipsilateral response (R2I) and second contralateral response (R2C) latencies in hypothyroidism were prolonged relative to controls, and the differences were statistically significant (P<0.001 and P<0.001, respectively). Latency of R1, R2I, and R2C did not correlate linearly free T3, free T4, or TSH values in the hypothyroid group. Conclusion: The finding of abnormal blink reflex responses in hypothyroid individuals raises the notion that they may be useful in detecting early changes and in the follow-up of the patients with the disorder.

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Introduction
Neurological dysfunction is an important consequence of hypothyroidism. Some of the neurologic manifestations of hypothyroidism include somnolence, lethargy, impaired memory and concentration, depression and entrapment neuropathy. Rarer but reversible neurological manifestations include cerebellar ataxia, psychosis, dementia and myxedema coma. Brainstem lesions are localized clinically, especially when they cannot be located on imaging techniques. The blink reflex (BR) is an electrical analogue of the clinically elicitable corneal reflex. Blink reflex is elicited by supramaximal stimulation of the has been widely studied in various pathological conditions affection the brainstem, facial and trigeminal nerves. Alteration of early R1 indicates a decrease in stimulus conduction due to an extrinsic pontine lesion or extrinsic compression of the pons or direct involvement facial or trigeminal nerves. Analysis of R2 is useful in distinguishing between lesions in the afferent or efferent pathways. Bilateral R2 delays reveal the presence of lesions somewhere along the afferent path (trigeminal nerve, spinal tract, trigeminal nucleus in the medulla and in pons). Unilateral R2 delay is present when there is a lesion somewhere along the efferent pathway (facial nerve or pons).

Electrophysiological evaluation of visual evoked potential has been performed in hypothyroid patients revealing the possibility of brainstem and cranial nerve dysfunction dysfunction in hypothyroid patients. As already mentioned above blink reflex can be possibly useful in documenting such abnormalities. Electrophysiological studies of blink reflex, with particular emphasis on the late responses, may be useful in revealing subclinical abnormalities of cranial nerves in metabolic diseases.

Methods
There were a total of 68 subjects out of which 20 were controls and 48 were patients suffering from hypothyroidism. The sample size was determined on the basis of data from previously published works. The study was carried out at the Dhiraj General hospital(Baroda). The patients included newly diagnosed cases with normal neurological examination who had yet not received any hormones as a part of the replacement therapy. Subjects with co-morbidities like cerebrovascular diseases and diseases involving cranial nerves, diabetes mellitus and other endocrine diseases, history of multiple sclerosis, history of psychiatric diseases and deficiency of vitamin B12 were excluded. Patients were divided into two groups: Subclinical and Overt hypothyroidism. Symptomatic patients with FT3 and FT4 below the normal limit (1.50–4.71 pg/mL and 0.80–1.90 ng/dL, respectively), with a TSH above normal (0.4–4.0 µIU/mL) formed the Overt group. Asymptomatic patients with normal FT3 and FT4 levels but elevated TSH levels formed the Subclinical group. Twenty control subjects with normal neurological exam and thyroid functions were selected. Exclusion criteria was same as above. All patients were explained the procedures that they are undergoing and made to sign an informed consent form.

All patients were subjected to a thorough clinical examination of all systems with special emphasis on neurological examination to exclude neurological abnormalities. Two clinicians independently clarified the findings. Fasting blood sugar (FBS) estimation was done using glucose oxidase method. Patients and subjects with FBS> 100mg% were excluded. Vitamin B12 levels were measured by Electroluminescence method. Subjects below 150 μg % were
excluded from the study. Serum FT3, FT4 and TSH were evaluated using chemiluminescence. The patients were divided into two groups subclinical hypothyroidism and overt hypothyroidism. The criteria for the diagnosis of overt hypothyroidism was FT3 and FT4 below the normal limit (1.50–4.71 pg/mL and 0.80–1.90 ng/dL, respectively), with a TSH above normal (0.4–4.0 idU/mL). Subclinical hypothyroidism is defined as normal serum FT3 and FT4 concentrations and an elevated serum TSH concentration. An electromyographic evaluation of the blink reflex was done in the patients. Subjects were made to lie supine on a bed in with eyes closed. Recordings were performed with a neuropack EMG machine, with a filter setting of 20 Hz to 10 kHz, using an analysis time of 50 ms with surface recording electrodes. The recording electrodes were placed over the orbicularis oculi muscle, at the lower eyelid. A reference electrode was placed over the orbicularis oculi muscle, on the lateral surface of the eye. The right and left supraorbital nerves were stimulated electrically 1 cm from midline at the supraorbital notch. The stimulus duration was 0.05 ms, with intensity 2 to 4 times greater than threshold.11 Two separate responses were elicited. Early response R1 which was unilateral at the side of stimulation, and late response R2 which was bilateral.12 The input was fed to a fast recovery amplifier with a frequency response of 10 Hz to 3 kHz, which allowed for accurate analysis of short latency responses. The latencies of the reflex responses were measured from the stimulus artifact to the initial deflection of the potential.13 For each subject, at least 10 recordings were obtained to get the shortest latency time R1 and R2 responses. A amplitude was considered an unreliable index and will not be used in any analysis.14

Statistical Evaluation

T test was done between R1/R2 latency times of the control subjects and hypothyroid patients.

Mann Whitney’s U-test was done between R1/R2 latency times of subclinical and clinical hypothyroidism.

P<0.05 was considered as statistically significant.

Results

Serum TSH levels were significantly higher and FT3 and FT4 levels lower in patients with overt hypothyroidism when compared with control subjects (P<0.001). Serum TSH levels were significantly higher in patients with subclinical hypothyroidism compared with control subjects (P<0.001). Serum vitamin B12 was similar in all groups (P>0.05). The mean serum concentrations of TSH, FT4, FT3, vitamin B12 for the patients and subjects are shown in Tables 1 and 2.

Clinically, patients of overt hypothyroidism complained of myalgia, fatigue, cold intolerance and cognitive changes (forgetfulness, inattention, apathy, and slowing of speech, movement, and mentation). Patients of subclinical hypothyroidism did not show these complaints. On examination patients of overt hypothyroidism had bradycardia, hypothermia and delayed relaxation of reflexes. Patients with subclinical hypothyroidism did not show these abnormalities.

Reflex response of the orbicularis oculi muscle to stimulation of the supraorbital nerve showed a double response in all control subjects. On the ipsilateral side, there was an early response (RI) with a mean latency of 10.6 ms and a second ipsilateral response (R2I) with a mean latency of 32.0 ms and a second contralateral response (R2C) with a mean latency of 34.0 ms.

### Table 1: Basic parameters in Subclinical Hypothyroidism patients and control Subjects

|                | Subclinical Hypothyroidism | Controls |
|----------------|----------------------------|----------|
| N              | 26                         | 20       |
| Age (years)    | 38.05 (10.5)               | 39.2 (11.6) |
| FT3 (pg/mL)    | 3.4 (0.7)                  | 3.5 (0.8) |
| FT4 (pg/mL)    | 1.4 (0.2)                  | 1.4 (0.2) |
| TSH (idU/mL)   | 9.5 (3.7)                  | 2.2 (0.6) |
| Vitamin B12 (ng/dL) | 280.5 (110) | 275.5 (120) |

Note: Values in Bracket indicate standard deviation. Values rounded off to first decimal place wherever appropriate.

### Table 2: Basic parameters in patients with Overt hypothyroidism and control Subjects

|                | Overt Hypothyroidism | Controls |
|----------------|----------------------|----------|
| N              | 22                   | 20       |
| Age (years)    | 40.5 (11.2)          | 39.2 (11.6) |
| FT3 (pg/mL)    | 1.4 (0.7)            | 3.5 (0.8) |
| FT4 (pg/mL)    | 0.6 (0.2)            | 1.4 (0.2) |
| TSH (idU/mL)   | 46.5 (24.2)          | 2.2 (0.6) |
| Vitamin B12 (ng/dL) | 312.2 (132) | 275.5 (120) |

Note: Values in Bracket indicate standard deviation. Values rounded to first decimal place wherever appropriate.

R2I and R2C latencies in hypothyroid subjects were prolonged relative to controls, in both overt and subclinical hypothyroidism and the differences were statistically significant (P<0.005 and P<0.005, respectively). The R2I (35.80 ± 2.2, 36.0 ± 2.4) and R2C (39.8 ± 3, 38.9 ± 2.20) latencies in both subclinical and clinical hypothyroid subjects were prolonged relative to control subjects. The differences were statistically significant (P<0.005 and P<0.005) (Tables 3 and 4). No significant latency difference was found for R1, R2I, or R2C in subclinical and clinical hypothyroid subjects (P>0.05). There was no correlation between the R1, R2I or R2C latencies and serum hormone level.

Discussion

Neurological dysfunction associated with disorders of the thyroid gland may be a result of hormonal imbalance or may be related to the immune mechanisms associated with thyroid diseases. The thyroid hormone affects the central and peripheral nervous systems via its role in gene expression, myelin production, its effects on the neurotransmitter system and axonal transportation. Overall neurological complications have been reported to be around 79% in hypothyroidism. Proximal muscle weakness, mental changes, constipation, intolerance to cold are some of the usual signs of hypothyroidism.

In our study, as expected, overt hypothyroid patients complained more about myalgia, fatigue, intolerance to cold and cognitive changes. The subclinical hypothyroid patients did not have these complaints.
Table 3: R1, R2I and R2C values in subclinical hypothyroids and control subjects

|         | Normal     | Subclinical Hypothyroids | p       |
|---------|------------|--------------------------|---------|
| R1(ms)  | 10.6 ± 1   | 10.7 ± .6                | >.05    |
| R2I(ms) | 32 ± 3.6   | 35.8 ± 2.2               | <.001   |
| R2C(ms) | 34 ± 3.5   | 39.8 ± 3                 | <.001   |

Table 4: R1, R2I and R2C Values in overt hypothyroids and control subjects

|         | Normal     | Overt Hypothyroids      | p       |
|---------|------------|-------------------------|---------|
| R1(ms)  | 10.6 ± 1   | 10.8 ± .7               | >.05    |
| R2I(ms) | 32 ± 3.6   | 36.0 ± 2.4              | <.001   |
| R2C(ms) | 34 ± 3.5   | 38.9 ± 2.2              | <.001   |

A high ratio of polyneuropathy (20–70%) associated with hypothyroidism has been reported and the mechanisms has been studied extensively. The metabolic alteration caused by hormonal imbalance affects the Schwann cell, inducing a segmental demyelination. Primary axonal degeneration has also been shown electrophysiologically and pathologically, only the function of the nerve is affected initially, but later structural alterations may also occur. Since the distal and sensory nerves are affected earlier, the most commonly involved nerves are the sural nerve and median nerve sensory fibers. Neuropathies involving the facial nerve have very rarely been reported in hypothyroid patients.

Blink reflex has two components: R1 and R2. Direct stimulation of the facial nerve produces a compound muscle action potential (CMAP) of the facial nerve. R1 is the short loop reflex, that occurs only on the side of stimulation. R2 is a longer loop reflex that occurs bilaterally. This response corresponds to the clinically observable blink. R2 responses were shortened in hyperthyroid individuals in research done by Bir et al.20 This finding can be explained with the inhibitor effect of excess thyroid hormone on the polysynaptic reflex arc of the BR and/or interneuronal excitability changes in the reflex arc in the brainstem of hyperthyroid subjects.22 Abnormalities in previous electrophysiological studies, which were reversed following replacement therapy, have been attributed to metabolic rather than structural alterations.6 Low body temp, diminished myelin production, and alteration in cerebral metabolism due to thyroid hormone deficiency may be the cause of these abnormalities.21

BR testing is an easy and noninvasive technique, which provides data that cannot be obtained with other clinical evaluations.22 The determination of normal BR in hypothyroid patients suggests that BR testing might be useful the evaluation and detection of subclinical CNS involvement in hypothyroid patients. We do not know whether or not these blink reflex abnormalities reflect an irreversible alteration caused by thyroid hormone deficiency. There could also be an autoimmune cause of these findings. We also do not know if hypothyroidism due to different etiologies would cause any difference in finding.

Whatever the mechanism, the finding of abnormal BR responses in hypothyroid subjects raises the possibility that they may be useful in detecting early changes and in the following of patients with the disorder.

Further studies could be designed to know if the blink reflex abnormalities caused are reversible or irreversible. Studies could be carried out to find out if the different etiologies of hypothyroidism (autoimmune, iodine deficiency etc) have any effect on blink reflex. Imaging studies could be carried out to see if any structural pontine lesion in the region of the circuitry can be visualized. Functional imaging studies (Nuclear imaging, functional Magnetic resonance imaging) could be carried out for visualization of the functional aspects of brainstem circuitry.

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