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Metin ÖZATA[1]
Abdullah ÖZKARDEŞ[2]
M. Ali GÜNDOĞAN[1]

Effects of Acute Hypothyroidism on Brainstem Auditory Evoked Potentials (BAEPs)

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Departments of [1]Endocrinology and Metabolism and [2]Neurology Gulhane School of Medicine, Etlik, Ankara-Turkey

Abstract: Although functional alterations in the central nervous system (CNS) and peripheral nerves are well documented in overt hypothyroidism, little is known about alterations of CNS in acute hypothyroidism. Sixteen patients with differentiated thyroid carcinoma were studied when prepared for radioiodine scanning after stopping levothyroxine (LT_4) therapy for 6 weeks to determine whether acute hypothyroidism leads to alteration in brainstem auditory evoked potentials (BAEPs). Repeat BAEPs were performed on the same patients at 6 months of the following L-T_4 therapy when patients were euthyroid. Neurophysiological findings were compared with a group of 20 normal controls with no hystory of thyroid disease. Wave I latency and I-III, III-V and I-V interpeak latencies in BAEPs were studied. A signifiant prolongation of wave I latency found in patients with acute hypothyroidism when compared to those in control subjects. Abnormal latencies were not correlated with thyroid hormone levels. These neurophysiologic abnormalities were completely restored to normal at 6 months after L-T_4 therapy. We conclude that acute hypothyroidism leads to reversible alterations in peripheral components of BAEPs. Our results also suggest that BAEPs could be useful tests to monitor functionale alteration of the central nervous system in acute hypothyroidism.

Key Words: Acute Hypothyroidism, BAEPs

Introduction

Thyroid hormone deficiency is associated with peripheral and central nervous system (CNS) dysfunctions (1-9). CNS manifestations include somnolence, lethargy, mental retardation, memory changes, depression, and rarely convulsions and coma (10). The CNS involvement in overt hypothyroidism has previously been shown on the basis of visual evoked potentials in adult patients (11-13) and of BAEPs and SSEPs in infants (14-16). However, little is known about quantitive changes in CNS after withdrawal of T4 in patients with thyroid cancer. We previously shown that subclinical hypothyroidism does not lead to alteration in BAEPs (17). However, no study reported the effects of acute hypothyroidism on BAEPs sofar.

The aims of the current study therefore were: to evaluate the alterations of CNS in acute hypothyroidism by recording BAEPs and to examine the reversibility of the alteration, if any, with L-T_4 treatment when patients were euthyroid.

Materials and Methods

BAEPs recordings were performed in 16 patients (6 male, 10 female; mean age 35.37±3.20 years) with thyroid carcinoma (10 had papillary and 6 had follicular cancer) when prepared for radioiodine scanning after stopping levothyroxine (L-T_4) therapy for 6 weeks. All patients were clinically and biochemically hypothyroid 6 weeks after withdrawal of L-T_4. The neurological examination was negative and all had a normal audiogram. Repeat BAEPs were recorded on the same patients at 6 months of the following LT_4 therapy when the patients were euthyroid. Neurophysiological findings before and after treatment were compared with a group of 20 normal controls with no history of thyroid disease (8 men, 12 female; age 32.25±3.07 years).

All subjects had given their informed consent for the present study. A history was taken and a complete medical examination including neurological examination was carried out for every patient. All patients and controls had a full medical and laboratory evaluation

(haematology, blood chemistry, urinalysisi) for exclusion of nonthyroidal illness. Serum levels of TSH, free thyroid hormones (fT_3, fT_4), and thyroid autoantibodies were measured in all patients and controls at the time of neurophysiological studies to assess the thyroid status.

None of the patients had a nonthyroidal illness, were taking medications or were pregnant. Also, none of the patients had other concurrent disorders or factors causing polyneuropathy or degenerative CNS disease such as diabetes mellitus, uraemia, collagen disease, cancer chemotherapy and anti-convulsant treatment. The patients or control subjects did not have a history of central nervous system disorder such as head injuri, congenital structural lesions, neurosurgical operations alcohol or drug abuse, and psychiatric illness.

Hormone measurement

Free T_3 (normal range: 2.2-4.7 pg/ml) and free T_4 (normal range: 0.85-2.67 ng/dL) were measured by radioimmunoassay (RIA) with reagents from Kodak Clinical Diagnostics Ltd. Amersham (Burcks, UK) (Kodak Amerlex-Mab fT_3 kit and Kodak Amerlex-Mab fT_4 kit, respectiavely). We determined serum TSH (upper limit of the normal reference interval was 6.5 mIU/mL) by an immunoradiometric assay (IRMA) from Medgenix Diagnostics SA (Fleurus, Belgium; TSH IRMA kit, coated-tube).

BAEPs recording

BAEPs recording was performed using surface EEG cup electrodes (silver chlodide electrodes, 10 mm cup, Nicolet Biomedical Instrument, Madison, WI, USA) and EEG paste (Ten 20 conductive EEG pate, Nicolett Biomedical Instrument, Madison WI, USA). BAEPs recording were carried out using Nicolett Compact Four electrodiagnostic system (Nicolett Biomedical Instrument, Madison, WI, USA). Impedance remained under 5kΩ at all times during sessions.

The EP signals were obtained simultaneously, ipsilaterally and contralaterally, by using reference electrodes located on both mastoids and an active electrode at the vertex. We report only ipsilateral records in this study. The ground electrode was placed on the forehead. Potentials were evoked by monaural auditory stimuli consisting of cliks of alternate polarity with a duration of 100msec, an intensity of 60 dB SPL higher than hearing threshold, and a stimulation frequency of 10 Hz via unshielded headphones (Nicolett Biomedical Instrument, Madison, WI, USA). Each potential was obtained from the average of 2000 responses for a 10 msec period.

The components studied were the latencies of peak I, and the interpeak intervals I-III, III-V and I-V for both ears.

All results are given as means±SD. The mean values for each electrophysiological parameter in patients with acute hypothyroidism and controls were compared using unpaired Student's t-test. BAEPs values before and at 6 months of the following LT_4 treatment were compared using paired Student's t-test. Correlation coefficients between hormone values and electrophysiological findings were calculated by Pearson's correlation test. A, $P<0.05$ was considered statistically significant.

Results

Mean serum fT_3, fT_4 and basal TSH concentrations for patients after stopping L-T_4 therapy for 6 weeks and control subjects are shown in Table 1. Serum free thyroid hormone levels were found to be decreased and patients were characterised by increased basal TSH values after stopping L-T_4 therapy. All patients were clinically and biochemically hypothyroid. At 6 months of the following L-T_4 therapy all patients are clinically euthyroid and fT_3, fT_4 and TSH levels were normal when repeated BAEPs were recorded.

Table 1. Serum levels of fT_3, fT_4 and TSH in patients after stopping LT_4 therapy for 6 weeks and in controls subjects

	fT_3 (pg/mL)	fT_4 (ng/dL)	Basal TSH (μIU/mL)
Patients	1.36±0.24*	0.31±0.13*	66.76±8.21*
Controls	3.45±0.69*	1.75±1.58*	3.51±1.42*

Values given are means ±SD,

* $p<0.001$ vs patient and control groups.

Table 2. Electrophysiological findings in patients with acute hypothyroidism before treatment and the controls

		Patients (n:16)	Controls (n:20)	P
BAEPs				
Right				
	I.Wave (msec)	1.72±0.25	1.55±0.10	0.023
	I-III IPL (msec)	2.18±0.30	2.07±0.23	NS
	III-V IPL (msec)	1.92±0.20	1.91±0.13	NS
	I-V IPL (msec)	4.11±0.20	3.99±0.26	NS
Left				
	I.Wave (msec)	1.78±0.30	1.58±0.12	0.022
	I-III IPL (msec)	2.19±0.22	2.13±0.18	NS
	III-V IPL (msec)	1.99±0.51	1.92±0.16	NS
	I-V IPL (msec)	4.21±0.47	4.06±0.27	NS

Values given are means ± SD

NS: not significant

Table 3. Electrophysiological findings in patients after stopping LT_4 therapy and at 6 months after commencement of LT_4 therapy

		Before treatment	After treatment	P
BAEPs				
Right				
	I.Wave (msec)	1.72±0.25	1.54±0.09	0.029
	I-III IPL (msec)	2.18±0.30	2.06±0.26	NS
	III-V IPL (msec)	1.92±0.20	1.91±0.15	NS
	I-V IPL (msec)	4.11±0.20	3.99±0.28	NS
Left				
	I.Wave (msec)	1.78±0.30	1.57±0.12	0.015
	I-III IPL (msec)	2.19±0.22	2.11±0.20	NS
	III-V IPL (msec)	1.99±0.51	1.92±0.16	NS
	I-V IPL (msec)	4.18±0.45	4.03±0.29	NS

Values given are means± SD

The electrophysiologic parameters in patients after stopping therapy and controls are shown in Table 2. A significant prolongation of wave I lacenty in BAEPs was found in patients with acute hypothyroidism when compared to those in control group. However, interpeak latencies in BAEPs did not yiield statistically significant differences between patient and control groups. L-T_4 therapy significantly reduced the mean right and left wave I latencies of BAEPs (1.72±0.25 to 1.54±0.09 msec, P=0.029 and 1.78±0.30 to 1.57±0.12 msec, P=0.015, recpectively) (Table 3). BAEPs recordings in a patient with acute hypothyroidism before therapy are shown in Figure 1.

There was no correlation between hormone levels and electrophysiological parameters.

Discussion

It is well known that overt hypothyroidism is associated with mononeuropathy or sensorimotor polyneuropathy due to primarily axonal damage or involvement of myelin (1-6). The electrophysiologic abnormalities such as slowing of motor and sensory nerve conduction velocities have been shown in overt

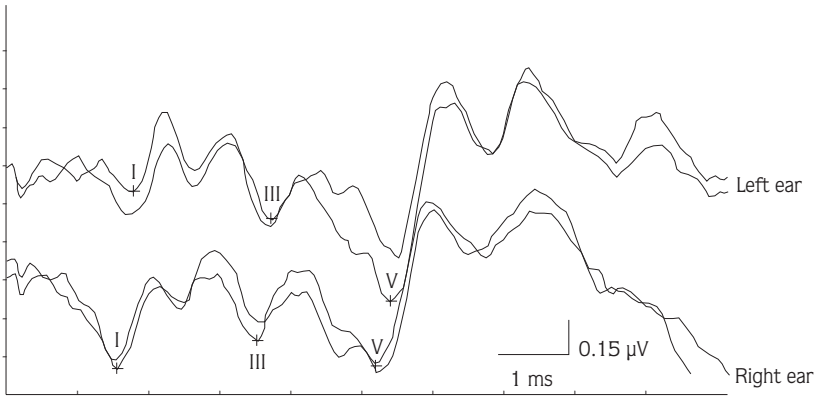

Figure 1. BAEPs recordings in a patient with acute hypothyroidism before treatment.

hypothyroidism (1-6). It is also known that thyroid hormones interfere with many of the processes in the nervous system (10). The CNS involvement in overt hypothyroidism has previously been shown on the basis of visual evoked potentials in adult patients (11-13) and of BAEPs and SSEPs in infants (14-16). However, little is known about quantitative changes in CNS after withdrawal of T4 in patients with thyroid cancer. Furthermore, no study reported the effects of acute hypothyroidism on BAEPs in adult patients to date. We therefore recorded BAEPs to assess the alteratinos of central nervous system in adult patients with acute hypothyroidism.

Brainstem auditory evoked potentials (BAEPs) have come into widespread use for assesment of the clinical state of the middle portion of the brainstem (18). BAEPs allow evaluation of the functional integrity of the auditory pathways, from the auditory nerve to the thalamic nuclei (18,19). Using this technique, we recorded BAEPs in our patients with acute hypothyroidism. A significantly increased wave I latencies was found, whereas interpeak latencies were normal. Our results show that acute hypothyroidism leads to peripheral deficit in BAEPs since wave I generated primarily by the VIIth nerve. Similarly, Laureau et al. (16,20) reported that congenital hypothyroidism causes the peripheral abnormalities in BAEPs. Increased wave I lacenty is indicative of delayed peripheral transmission. Since our patients had normal audiogram, finding of a delayed wave I latency is due to acute hypothyroidism but not inner ear or coclear abnormalities. Reversibilty of abnormal wave I latency after restoration of euthyroidism also support that the T_4 deficiency is responsible for the wave I abnormalities in BAEPs. However, it is not clear why impairment of interpeak latencies were not observed in acute hypothyroidism. It is possible that peripheral components of BAEPs are more sensitive to thyroid hormone deficiency.

Low body temperature, diminished myelin production and alteration in cerebral metabolism during acute hypothyroidism may be the possible explanations for the prolongation of wave I latency. The influence of low temperature in acute hypothyroidism could be considered because hypothermia in adult patients with overt hypothroidism causes an additional slowing of both peripheral and central conduction (21). Thyroid hormone is known to influence the synthesis of proteins and production of enzymes and myelin (10). Thus acute hypothyroidism may cause the diminished myelin synthesis (22). A recent study (23), using P-31 nuclear magnetic resonance (NMR) spectroscopy, also demonstrated that acute hypothyroidism in patients with thyroid cancer after withdrawal of L-T_4 leads to reversible alterations in adult cerebral phosphate metabolism.

We did not find any correlations between serum fT_4 and BAEPs parameters. The several factors, such as a nonlinear relation between serum T_4 and the 5'deiodinase activity, the interference of the T_4 blood-brain barrier and time lag between T_4 and BAEPs alterations, may disturb direct relation.

Initial abnormal components of BAEPs in patients with acute hypothyroidism were completely restored to normal at 6 months of the following LT_4 therapy. Thus, the present study indicates that acute hypothyroidism leads to reversible abnormalities of peripheral components of BAEPs. These results also reflect an effect of acute thyroid hormone deficiency on the CNS. Reversible alteration of the CNS functions has previously been shown by using visual evoked responses in patients with overt hypothyroidism (11-13). However, we have the first to show reversible altearations of CNS in adult patients with acute hypothyroidism by using BAEPs.

We conclude that acute hypothyroidism leads to reversible alterations in central nervous system as determined by BAEPs recordings. Our results also suggest that BAEPs could be useful tests to monitor functional alteration of the central nervous system in acute hypothyroidism.

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References

1. Nemni R, Bottacchi E, Fazio R, Mamoli A, Corbo M, Camerlingo M, Galardi G, Erenbourg L, Canal N. Polyneuropathy in hypothyroidism: Clinical, electrophysiological and morphological findings in four cases. J Neurol Neurosurg Psychiatry 50:1454, 1987.
2. Rao SN, Katiyar C, Nair KRP, Misra S. Neuromuscular status in hypothyroidism. Acta Neurol Scandinav 61:167, 1980.
3. Beghi E, Delodovici M, Bogliun G, Crespi V, Paleari F, Gamba F, Capra M, Zarrelli M. Hypothyroidism and polyneuropathy. J Neurol Neurosurg Psychiatry 52:1420, 1989.

4. Torres CF, Moxley RT. Hypothyroid neuropathy and myopathy: Clinical and electrodiagnostic longitudinal findings. J Neurol 237:271, 1990.

5. Dick DJ, Nogues MA, Lane RJM, Fawcett PRW. Polyneuropathy in occult hypothyroidism. Postgrad Med J 59:518, 1983.

6. Pollard JD, Mcleod JD, Honnibal TGA, Verheijden MA. Hypothyroid polyneuropathy. J Neurol Sci 53:461, 1982.

7. Gold MS, Pottash ALC, Extein I. Hypothyroidism and depression: Evidence from complete thyroid function evaluation. JAMA 245:1919, 1981.

8. Neeck G, Riedel W, Schmidt KL. Neuropathy, myopathy and destructive arthropathy in primary hypothyroidism. J Rheumatol 17: 1697, 1990.

9. Shirabe T, Tawara S, Terao A, Araki S. Myxoedematous polyneuropathy: A light and electron microscopic study of the peripheral nerve and muscle. J Neurol Neurosurg Psychiatr 38: 241, 1975.

10. DeLongs GR, Adams RD. The neuromuscular system and brain in hypothyroidism. In: Braverman LE, Utiger RD (eds), Werner and Ingbar's The Thyroid 6th ed JB Lippincott Co., Philadelphia pp 1027, 1991.

11. Avramides A, Papamargaritis K, Mavromatis I, Saddic G, Vyzantiadis A, Milonas I. Visual evoked potentials in hypothyroid and hyperthyroid patients before and after achievement of euthyroidism. J Endocrinol Invest 15: 749, 1992.

12. Ladenson PW, Stakes JW, Ridgway EC. Reversible alteration of the visual evoked potentials in hypothyroidism. Am J Med 77: 1010, 1984.

13. Mastaglia FL, Black JL, Collins DWK, Gutteridge DH, Yuen RWM. Slowing of conduction in visual pathway in hypothyroidism. Lancet 18: 387, 1978.

14. Bongers-schokking CJ, Colon EJ, Hoogland Ra, DeGroot CJ, Brande JLW. Somatosensory evoked potentials in neonates with primary congenital hypothyroidism during the first week of therapy. Pediatr Res 30: 34, 1991.

15. Bongers-schokking CJ, Colon EJ, Mulder PGH, Hoogland RA, DeGroot CJ, Brande JLW. Influence of treatment on the maturation of the somesthetic pathway in infants with primary congenital hypothyroidism during the first year of life. Pediatr Res 34: 73, 1993.

16. Laureau E, Vanasse M, Hebert R, Letarte J, Glorieux J, Desjardings M, Dussault JH. Somatosensory evoked potentials and auditory brainstem responses in congenital hypothyroidism. I a longitudinal study before and after treatment in six infants detected in neonatal period. Electroenceph Clin Neurophysiol 64: 501, 1986.

17. Özata M, Özkardep A, Çorakçi A, Gündogan MA. Subclinical hypothyroidism does not lead to alteration either peripheral nerves or in BAEPs. Thyroid 5:201, 1995.

18. Nuwer MR, Aninoff M, Desmedt J, Eisen AA, Goodin D, Matsuoka S, Mauguiere F, Shibasaki HS, Sutherling W, Vilbert J-F. IFCN recommended standards for short latency somatosensory evoked potentials. Electroencephalograph Clin Neurophysiol 91:6, 1994.

19. Hashimoto I. Critical analysis of short-latency auditory evoked potential recording techniques. In Luders H(eds), Advanced Evoked Potentials. Kluwer Academic Publishers, Boston, MA p 105, 1989.

20. Laureau E, Hebert R, Vanasse M, Letarte J, Glerioux J, Desjardins M, Dussault JH. Somatosensory evoked potentials and auditorybrainstem responses in congenital hypothyroidism. II a cross-sectional study in childhood. Correlations with hormonal levels and developmental quotients. Electroenceph Clin Neurophysiol 67: 521, 1987.

21. Abbott RJ, O'Mallye BP, Barnett DB, Timson L, Rosenthal FD. Central and peripheral nerve conduction in thyroid dysfunction: The influence of L-thyroxine therapy compared with warming upon the conduction abnormalities of primary hypothyroidism. Clinical Science 64: 617, 1983.

22. Bhat NR, Shanker G, Pieringer RA. Investigations on myelination in vitro: regulation of 2,3'-cyclic nucleotide 3'-phosphohydrolase by thyroid hormone in cultures of dissociated brain cells from embryonic mice. J Neurochem 37: 695, 1981.

23. Ain KB, Smith CD. Effects of acute hypothyroidism on human brain phosphorus metabolism. 67th Annual Meeting of ATA. September 28-October 1 1994, Thyroid 4 (Supl 1): abstract no 13, 1994.