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Neurocognitive functions and some electrioencephalographic changes in preadolescent children with different degrees of primary hypothyroidism and mild iodine deficiency

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Abstract

Neurologic and electrophysiologic changes in children with mild hypothyreosis and euthyroid goiter at the background of mild ID are not well understood at present. Our goal was to evaluate of some cognitive disturbances and alteration of some EEG parameters in preadolescent children at early stages of the development of primary hypothyreosis and euthyroid goiter. 55 somatically healthy preadolescent children, aged 8-12 years with the 1st degree of diffuse goiter underwent clinical and neurological investigation of cognitive functions: "copy", "time to copy" and "recognition" using Rey Complex Figure Test and recognition trial as well as Rochester fatigue Diary test; Motor Fatigue index, PASAT – 3 (second version) and lassitude was evaluated. Digital 21 channeled EEG study was also performed. Study groups were randomized to: children with overt mild hypothyreosis; children with subclinical hypothyreosis; euthyroid children; healthy controls. Mediana of UIE 64 was in the lower 3rd in the range for mild ID. Children of the study group more often had non-specific neurologic symptoms. All indices of neurocognitive dysfunction were more frequent in

patients with overt hypothyreosis (P<0,001) and in lesser extent were present in subclinical hypothyreosis and euthyroid goiter, compared to controls. This was accompanied by the changes of EEG parameters. The pathologic visual version of EEG had 90% of children with overt hypothyreosis. In turned out that in prepubertal children is accompanied by cognitive disorders represented by Mild Cognitive Impairment; among neurologic subclinical signs of manifestation of ID the Fatigue test is of great sensitivity; even mild ID is characterized by specific changes of the frequency and amplitude of physiologic spectrum of EEG activity, mainly of aA; pathologic consequences of ID are manifested both in overt and subclinical hypothyroidism and in lesser extent in patients with euthyroid goiter.

KEY WORDS: Neurocognitive functions; "copy"; "time to copy"; "recognition"; hypothyroidism

Introduction

Generally, among regional population with iodine deficiency (ID) there is a high prevalence of various types of thyroid dysfunction, especially, primary hypothyroidism (PH) which is regarded as one of the most important causes of mental retardation. Therefore, population from these regions has lower IQ as compared to those from iodine-sufficient areas [1]. This was explained by the profound effect of thyroid hormones on developing brain and anatomy and physiology of peripheral nerves and dramatic consequences of even mild thyroid insufficiency on mental function in future life [2].

From ancient past Georgia belongs to the group of countries where significant regions are represented by ID regions. Epidemiologic studies carried out at the end of the last century revealed high prevalence of goiter among pre-adolescents 31-93% [3] at the background of moderate and severe ID and 64% in 2004 [4]. Things have changed at the beginning of XXI century after introduction of mandatory salt iodization in Georgia with the help of WHO and UNICEF in 2005. Since then severe ID has been eliminated [5].

Recent academic papers are full of information concerning clinical manifestations of overt and severe PH in newborns, children and adults [6]. But less is known about psycho-neurological and electrophysiological changes in preadolescent children with moderate and latent forms of PH and euthyroid goiter developed in the regions with mild ID. Present data are scarce and equivocal. At the same time most authors con-

cluded that even minimal ID in vulnerable periods of life: pregnancy, neonatal and early childhood period, puberty, stress, etc. may give impetus to the development of minimal thyroid insufficiency or so-called asymptomatic hypothyroxinemia with FT4 at low normal level and TSH at high normal [7]. Prolonged ID may also cause decrement of the ability of thyroid gland to synthesize and produce thyroid hormones [8].

Our aim was to study aims at finding peculiarities of neuroendocrine functions in preadolescent children aged 8-12 from mild ID areas of Georgia with different degrees of PH to reveal early latent symptoms of the disease.

Materials and methods

The work has been performed with the help of the Ministry of Health and Welfare and assistance of the Georgian charity organization ″SOCO″.

Overall, 100 preadolescent otherwise healthy children underwent complex clinical investigation. Consilium of pediatricians, neurologists, endocrinologists and surgeons made a decision concerning their health.

Clinical investigations were performed as a part of epidemiological studies in the schools of 15 regions of Georgia. Laboratory and EEG investigations were conducted in corresponding department's hospitals in Georgia.

Urinary iodine excretion (UIE) was measured by the biochemical method with the use of special KITs. The values were taken in Mkg/L. Blood FT4 and TSH levels were measured by the immune-ferment method using apparatus ELISA taken in ng/dl and mU/L, respectively.

The degree of goiter was evaluated using WHO criteria, last version.

Ultrasound investigation of thyroid gland with the apparatus ALOKA – 210.

Rochester Fatigue Diary (RFD) test was used to reveal the fatigue phenomenon.

Electroencephalographic (EEG) investigation was performed on digital 21 channel encephalograph ″Braintest″.

Mnestic – Cognitive function of the brain was studied by Rey Complex Figure Test and Recognition Trial [9].

Three components of the test were evaluated:

1. ″copy″ – ability to copy geometrical construction;
2. ″time to copy″ evaluation of time for ″copy″;
3. ″recognition″ tests the visual-spatial perception ability, attention and visual-spatial memory.

Evaluation of functional neurological status was made with the use of Rochester Fatigue Diary. Namely, its three components:

1. Motor Fatigue index;
2. Paced Auditory Serial Addition test (PASAT3.2). The test evaluates attention and the fast line of information processing by calculating correct and incorrect answers following listening of information during three minutes. More than 10% of incorrect answers are indicative for cognition tiredness;
3. ″Lassitude″. Is subjective and is evaluated by persons investigated. Answers are compared to the control group.

Motor fatigue index was calculated only for extensor ulnar muscle and for flexor muscle of the hand.

Electroencephalography (EEG) was performed with 21-channal digital apparatus ″Braintest″. Both visual and computer analysis were made. Brane electromagnetic potentials were divided according to their frequency ranges measured in – Hz: D – Delta wave – 2-4 Hz; T-Theta wave – 4,0-8,0 Hz; A – Alpha wave – 8,0-13Hz; B – Beta wave 14,00-30,0 Hz EEG of healthy children of 0-12 months are represented by slow waved D rhythm and till six-year-old children with slow waved T rhythm.

As for healthy adolescents, nearly 90% of their basic EEG rhythm revealed in sober state at rest with closed eyes or in dark is regular – synchronized A rhythm, of 8-13 Hc frequency with 20-90 mcv^2 range and Index of distribution (i)>50%.

So, a rhythm is the basic rhythm of six or more aged persons and it is associated with intuitive-conscious thinking psycho-emotional stability. Decrement of iA on more than 50% and significant deviation of its amplitude from the normal level is directly associated with psychomotor development retardation and the development of pathological behavior.

Amplitude (a) is magnitude, expressed in MKV^2, of measured from pic to pic and normally aA rhythm is 20-110 mkv^2.

Index (iA and iT) is a time, expressed in %, of being of given EEG activity in given EEG epocha.

Visual evaluation of EEG data was made by classification of Zhirmunskaia [10]), which relies on Alfa rhythm data, and five groups were identified:

- Normal variant – organized type. The A rhythm is predominant in the occipital region with Normal amplitude (aA>40 and iA>50%) small low wave activity with amplitude less than of basic A rhythm;
- Disintegrated type (disorganized), characterized by the presence of A rhythm, but with significantly lesser index, compared to norma (<30% iA<50%) slow waves are represented in more amount;
- Desynchronized type-with less amplitude oscillations (<30mkv^2) and frequent various low amplitude rhythmic activities. iA is very low (<30%).

- Mixed – desynchronized-disintegrated type is pathologic type with the absence of A rhythm and presence of slow activity in the form of T and D rhythms.

Statistical analysis was made by multicentre variable method chosen from computer management system EPINFO.

Results and Discussion

From the whole cohort of prepubertal children we choose 55 with 1st degree goiter, aged 8-12 years and randomized them in three groups and controls:

1. Group I – 12 children with mild overt PH (FT4 0.7 – TSH – 10.5);
2. Group II – 22 children with subclinical hypothyreosis – (FT4 1.1 – TSH – 4.2);
3. Group III – 21 children with euthyroid state (FT4 1.3 – TSH-3.1);
4. Group IV – 15 control healthy children with normal (FT4 1.5 – TSH – 2.8).

Medina of UIE in the areas they leaved was 60.4; 10th percentile – 50.20 and 90th percentile 74.5. This numbers are in the lower third of the range for mild ID.

Study groups had following complaints. Their percentage distribution you can see in Table 1. ″Copy″ test results clearly illustrate that a considerable amount of children of group I and group II 23.8% and 18.6% ($P<0.01$ and $P<0.05$), respectively had mnestic cognitive dysfunction. It was less common in the group III 15% and 4.76 in controls.

Motor Fatigue Index in group I and group II was the highest in group I as compared to control and did not differ substantially between the study groups ($P>0.5$). This indicates that not only patients with overt hypothyreosis but also those with lesser degree of thyroid insufficiency and even euthyroid group show deterioration of cognitive functions.

PASAT test indicating of cognitive tiredness was more frequently altered in group I 16.6% as compared to group II and III 10.5 and 9.0%, $P<0.01$ and $P<0.001$, respectively, and controls 4.54%, $P<0.001$.

″Time to copy″ was disturbed in 12% of group I, 9% of group III, 7% of group III and 3.12% of controls ($P<0.00$, $P<0.011$, $P<0.05$, respectively).

″Recognition″ test also revealed altered cognition in 15.6% of group I and to a Lesser extension in groups 2 and 3 – 10.1 and 8%, respectively, as compared to controls 3.12% ($P<0.001$).

Thus, from the results observed alterations of cognition functions in preadolescent children can be considered as ID induced early neurological equivalents that precede manifestation of clinical neuroligical symptoms.

Data achieved are consistent with the results of experiments which presented the evidence that Hypothyroxinemia of pregnant women causes cognitive dysfunction in their children [11] and even mild iodine deficiency of mothers is followed by cognitive and psychomotor changes in progeny.

According to the results of EEG investigation, 66.6% of controls had a normal type of the curve with predominant A rhythm of 9-12 Hc frequency and moderate level of amplitude 90-110 mcv2. Besides, single T waves in central and occipital areas were found. 27.7% of healthy children had disorganized EEG type and 9.09% desynchronized type.

No child with overt PH had a normal type EEG. 33.3% show the disorganized type, 33.3% demonstrate a desynchronized one and 33.3% showed a mixed type.

The same picture was found in patients with subclinical hypothyreosis with significant lower levels of EEG types 18.1%, 20.2% and 17% P<0.01, P<0.01, P<0.01), respectively.

Children with euthyroid goiter had a normal type of EEG in16.66% of cases, 23.3% disorganized type and 60% desynchronized. Obtained data show the highest prevalence of pathologic EEG types in overt hypothyreosis. These changes were less common in subclinical hypothyreosis and patients with euthyroid goiter. So, overt hypothyreosis has more pronounced negative effect on the brain functional ability and is manifested by the prevalence of desynchronized EEG.

Computer analysis of EEGI revealed a significant p<0.01 increase of interrelation of iT/iA 2.54 in overt hypothyreosis, compared to controls – 1.9 and decrease P<0.01 of aA max 103.4 mkv2 compared to controls 110.10 mkv2. These changes were less pronounced in subclinical hypothyreosis and eutyroid group – 100 and 105 respectively.

So, EEG confirms the damaging effect on the brain function of preadolescent children not only in overt hypothyreosis but also in a subclinical form and euthyroid goiter. These data are consistent with [12] presenting experimental evidence of significant and proportional decrement of cerebral blood flow in severe hypothyroidism of short duration followed by direct effect on the overall brain activity.

Table 1. *The percentage distribution of complaints in patients*

Headache	18.6%
Neurotic state (irritability, emotional lability, squeamishness)	17.5%
Sthenic syndrome (adynamia, weakness, easy tiredness)	14.1%
Sleep disturbances (anxiety, restless sleep)	22%
Memory impairment	8.6%
Palpitation	7.7 %
Coldness and numbness of the limbs	7.5%

Conclusion

So, based on our data, we can conclude that mild ID in prepubertal children is accompanied by cognitive disorders represented by Mild Cognitive Impairment; among neurologic subclinical signs of manifestation of ID the Fatigue test is of great sensitivity; even mild ID is characterized by specific changes of the frequency and amplitude of physiologic spectrum of EEG activity, mainly of aA; pathologic consequences of ID are manifested both in overt and subclinical hypothyroidism and in lesser extent in patients with euthyroid goiter.

The significance of such studies is of a basic and applied nature, therefore, coordinated studies of representatives of different specialties in this direction are very important. To this end, we continue similar studies, including a large number of patients, involving specialists from related fields.

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