Sokolnyk Snizhana Vasylivna, Kolesnik Dmytro Ivanovych, Nechytaylo Dmytro Yuriyovych, Sokolnyk Iryna Serhiivna, Khlunovska Lyudmyla Yuriivna, Loziuk Iryna Yaroslavivna, Ostapchuk Valentyna Hryhorivna. Indicators of cognitive activity of children with laboratory hypothyroidism. Journal of Education, Health and Sport. 2021;11(10): 301-310. eISSN 2391-8306. DOI http://dx.doi.org/10.12775/JEHS.2021.11.10.028
https://apcz.umk.pl/JEHS/article/view/JEHS.2021.11.10.028
https://zenodo.org/record/5717279

The journal has had 5 points in Ministry of Science and Higher Education parametric evaluation. § 8. 2) and § 12. 1. 2) 22.02.2019.

Received: 30.09.2021. Revised: 12.10.2021. Accepted: 29.10.2021.

INDICATORS OF COGNITIVE ACTIVITY OF CHILDREN WITH LABORATORY HYPOTHYROIDISM

[1]Snizhana Vasylivna Sokolnyk, [1]Dmytro Ivanovych Kolesnik,
[2]Dmytro Yuriyovych Nechytaylo, [1]Iryna Serhiivna Sokolnyk,
[1]Lyudmyla Yuriivna Khlunovska, [1]Iryna Yaroslavivna Loziuk,
[1]Valentyna Hryhorivna Ostapchuk

[1]Department of Pediatrics and Medical Genetics Bukovinian State Medical University, Chernivtsi, Ukraine
[2]Department of Pediatrics, Neonatology and Perinatal Medicine of Bukovinian State Medical University, Chernivtsi, Ukraine

Address for correspondence: Sokolnyk Snizhana Vasylivna, head of the department of Pediatrics and Medical Genetics, DMS, MD, professor; e-mail: Sokolnyk.Snizhana@bsmu.edu.ua
https://orcid.org/0000-0002-9399-4010

Abbreviation
IDD - Iodine deficiency disorders
HL - Laboratory hypothyroidism
TSH - Thyroid stimulating hormone
TRH - Thyrotropin - releasing hormone

Abstract

The growth rate of a healthy child, the peculiarities of its physical and intellectual development, the formation of reproductive function are largely determined by the state of the endocrine system. Thyroid hormones have a significant impact on the growth and development of the child's organism. Today, attention is focused on the consequences of

intellectual disabilities in children with hypothyroidism, as well as the impact of chronic iodine deficiency in the environment on the development of children. Insufficient intake of iodine in the body leads to congenital dysontogenesis of higher mental functions, to the formation, in severe cases, of mental retardation of varying degrees, and, in mild forms - to the borderline or partial disorders of intelligence.

The **aim** is to study the cognitive functions of children with laboratory hypothyroidism.

Methods. For a screening study of the intellectual development of school-age children living in geographical areas of Chernivtsi region (Ukraine) with varying degrees of iodine supply, 399 schoolchildren aged 11-18 years were studied, including 194 boys and 205 girls. The main group consisted of children (99) with laboratory hypothyroidism (HL), with thyroid stimulating hormone (TSH) elevation or with diverse complaints and who had been found to have elevated TSH levels during routine examinations. Patients with any kind of systemic disease and/or taking medications were excluded from the study. Diagnosis of HL was based on mild increase of TSH (5-25mIU/L) with a normal fT4 level. Thyrotropin-releasing hormone (TRH) test was also performed in all children. TSH response to TRH stimulation was considered to be normal when TSH levels were between 5-25 mIU/L. The formation of intellectual function was determined using a fragment of the R. Kettel test (adapted modified version of the children's personality questionnaire R. Kettel).

Inclusion criteria: age 11-18 years, living in the Chernivtsi region, the absence of organic pathology of the CNS and mental retardation, diseases of the eyesight and hearing, for 6 months, all subjects did not receive any treatment with iodine-containing drugs and thyroid hormones.

Results. Analysis of the study results showed that children, for the most part, have an average degree of intellectual development (60%). The level of intellectual formation changed in the direction of decreasing with increasing degree of iodine deficiency. Among children with laboratory hypothyroidism, the number of those who had a low level of intelligence was almost twice as high as in children from the comparison group 25 [21.8-27.3] % against 13 [11.8-16.6] %, $P < 0.01$). Children with laboratory hypothyroidism have a "debt" of 56% of attention, 36% of perception, 26% of motility, and 44% of memory. The pace of operating activities was reduced by 26%. Comparison of TSH concentration, ioduria and thyroid volume with the presence or absence of deficits in certain cognitive functions showed that in children with laboratory hypothyroidism and fine motor skills TSH G level was increased by 90%, thyroid volume by 28% , and with memory loss - 125% and 38%, respectively.

Correlative analysis revealed a highly probable positive relationship between moderate strength in prepubertal children between thyroid volume and fine motor skills ($r = 0.485$, $P < 0.01$), memory ($r = 0.488$, $P < 0.05$) and efficiency ($r = 0,321$, $P < 0,05$).

Conclusion. Children with subclinical hypothyroidism are characterized by decreased memory, instability of attention and decreased ability to concentrate, impaired fine motor skills, which generally reduces their mental capacity.

Key words: children; iodine deficiency; subclinical hypothyroidism; cognitive parameters

Mental development, being a dynamic system, depends on both the assimilation of social experience and the maturation of the organic basis (brain and nervous system in the first place). The growth rate of a healthy child, the peculiarities of its physical and intellectual development, the formation of reproductive function are largely determined by the state of the endocrine system [1]. Thyroid hormones have a significant impact on the growth and development of the child's body [2].

It is known that one of the reasons that can lead to impaired neuro - mental development of children is insufficient intake of iodine, resulting in reduced production of thyroid hormones [3]. Iodine deficiency is the cause of mental retardation in 42 million people. In areas where iodine prophylaxis is not carried out, each subsequent generation has an intellectual level for 10 - 15 points lower than the previous one [4, 5].

The most common consequence of iodine deficiency in children, in addition to endemic goiter, is a complex of psychomotor and somatic disorders. Living in areas with iodine deficiency, even with euthyroid goiter, is accompanied by reduced reproduction of auditory information, deterioration of visual memory, mental activity, adaptive capacity of the central nervous system [6].

It is established that against the background of chronic iodine deficiency in 30 - 60% of children there are behavioral, emotional disorders, personality disorders.

Iodine is needed at all stages of formation and functioning of the nervous system of the fetus, child, adult. Insufficient intake of iodine in the body leads to congenital dysontogenesis of higher mental functions, the formation in severe cases of mental retardation of varying degrees, and in mild forms - borderline or partial disorders of intelligence [7].

A number of authors [8-10] focus on the consequences of intellectual disabilities in children with hypothyroidism, as well as predict the impact of chronic iodine deficiency in the environment on children's development.

Hypothyroidism is a metabolic condition that can lead to cognitive and behavioral deficits in children and adolescents [11]. Current data suggest that early diagnosis and treatment of hypothyroidism improves cognitive functions [12-14]. It has been suggested that l hypothyroidism laboratory (HL), characterized by mild increase in serum thyrotropin (TSH) together with a normal serum free thyroxine (fT4) level, is a risk factor for development of systemic diseases such as atherosclerosis, cardiovascular diseases as well as neuropsychiatric disorders.

However, despite the wide range of research in this area over the last decade, most aspects of this problem remain understudied. This is especially true in the clinical stages of the development of health disorders.

The aim is to study the cognitive functions of children with laboratory hypothyroidism.

Methods. For a screening study of the intellectual development of school-age children living in geographical areas of Chernivtsi region with varying degrees of iodine supply, 399 schoolchildren aged 11-18 years were studied, including 194 boys and 205 girls. The main group consisted of children (99) with laboratory hypothyroidism (HL), with TSH elevation or with diverse complaints and who had been found to have elevated TSH levels during routine examinations. Patients with any kind of systemic disease and/or taking medications were excluded from the study. Diagnosis of HL was based on mild increase of TSH (5-25mIU/L) with a normal fT4 level. Thyrotropin-releasing hormone (TRH) test was also performed in all children. TSH response to TRH stimulation was considered to be normal when TSH levels were between 5-25 mIU/L.

Assessment of children's development was performed after acquaintance with the state of their health, exclusion of mental disorders and neurological pathology, assessment of the auditory and visual analyzers (according to the review of relevant specialists). The formation of intellectual function was determined by the usage of the R. Kettel test fragment (adapted modified version of the children's personality questionnaire R. Kettel) [3]. The methodology was constructed of 10 questions, where the correct answer was evaluated in one point. The sum of points was translated into standard grades - "score" which determined the low (1-3 score), medium (4-7) and high (8-10) level of intelligence. Statistical processing included calculating the arithmetic mean of each of the indicators (M), the standard deviation (σ). The evaluation of the probability of the results involved determining the mean error of the arithmetic mean (m), the probability of differences in the mean values by t - Student's test. The computer program "Biostat" was used for statistical processing.

The authors assert that all procedures contributing to this study comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the Bukovinian State Medical University.

Results. The distribution of children by area of residence is presented in Table 1.

Table 1

The distribution of children by area of residence

Area of residence	Total								
	11	12	13	14	15	16	17	18	Total
Chernivtsi	16	16	14	11	16	24	18	16	131
Mountain area	21	24	23	11	16	17	10	19	141
Plain area	19	19	12	25	15	18	11	8	127
Together	56	59	49	47	47	59	39	43	399

Total Analysis of the results of the study showed that children, for the most part, have an average degree of intellectual development (60%). The level of intellectual formation changed in the direction of decreasing with increasing degree of iodine deficiency. Thus, in children living in the zone of mild iodine deficiency (plain area and Chernivtsi), the share of children with a high level of development was 15 [DI 11.2-23.8] %, while in children from the area of residence with moderate degree of iodine deficiency (mountain area) - 9 [DI 8,3 - 9,2]% of children ($P < 0,05$).

Analysis of the development of intellectual functions depending on the area of residence and gender showed that among children living in mountainous areas, a high level of intelligence was determined in 10 [DI 7.8-12.5]% of boys and 13 [DI 9.2-15.6]% of girls, average - respectively in 45 [DI 39,5-47,8]% of boys and 51 [DI 48,8-55,7]% of girls and low - in 42 [DI 39,7-45,2] % of boys and 35 [DI 31.9-38.5]% of girls. Children living in the plains according to the level of development of intellectual functions were distributed as follows: high level - in 20 [DI 19.3-22.8]% of boys and 17 [DI 15.9-18.8]% of girls, medium - 58 [DI 52.9-59.9]% of boys and 62 [DI 54.1-67.6]% of girls and low - 21 [DI 18.3-23.8]% of boys and 21 [DI 19, 9-23.8]% of girls.

Children with high and medium level of intelligence development had sufficiently developed abstract forms of thinking, a large amount of knowledge. Children with a low level of intelligence were dominated by a primitive approach to solving logical problems, they were dominated by specific forms of thinking.

Among children with laboratory hypothyroidism, the number of those with low levels of intelligence was almost twice as high as in children in comparison group 25 [DI 21.8-27.3]% vs. 13 [DI 11.8-16.6] %, P <0.01).

Also noteworthy is the much smaller proportion of children with laboratory hypothyroidism with a high level of intellectual development (Fig. 1).

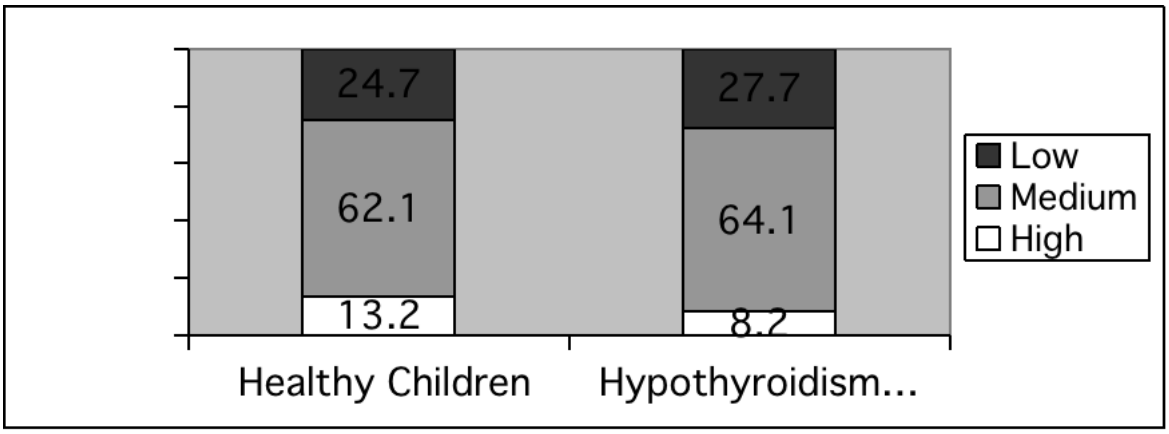

Fig. 1 The level of formation of intellectual functions in children

The structure of cognitive deficiency in children of the main group is presented in Fig. 2. Indicators of cognitive functions of children in the comparison group are taken as 100%. It is established that children of the main group are characterized by slightly lower indicators of basic cognitive functions. Thus, children with laboratory hypothyroidism have "debt" in the field of attention by 56%, perception by 36%, motility by 26%, memory by 44%. The pace of operating activities is reduced by 26%. Comparison of TSH concentration, ioduria and thyroid volume with the presence or absence of deficiency in certain cognitive functions showed that in children of 2 subgroups with motility disorders TSH level was increased by 90%, thyroid volume by 28%, and with reduced memory - 125% and 38% respectively. Indicators of cognitive functions of children in the comparison group are taken as 100%. Comparison of thyroid hormone concentrations, ioduria and thyroid volume with the presence or absence of deficiency in certain cognitive functions showed that in children with laboratory hypothyroidism and motility disorders, the level of thyroid-stimulating hormone was increased by 90%, the volume of the thyroid gland %, and with memory loss - 125% and 38%, respectively.

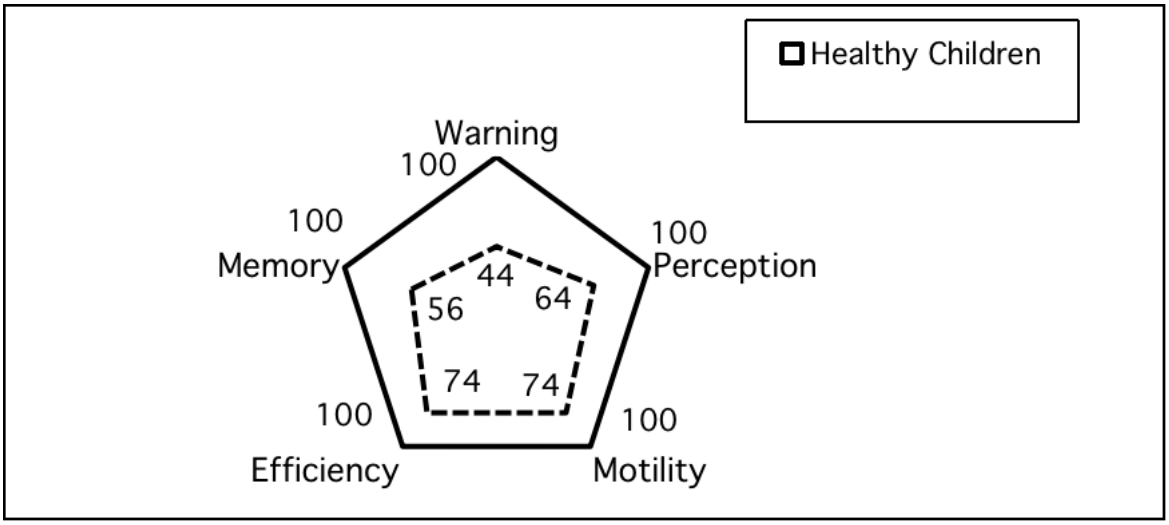

Fig. 2 Indicators of cognitive function in children of the main group (in % to the age norm)

Correlative analysis revealed a highly probable positive connection between moderate strength in prepubertal children between thyroid volume and fine motor skills (r = 0.485, P <0.01), memory (r = 0.488, P <0.05) and efficiency (r = 0,321, P <0,05).

Discussion. The development of children's psychoemotional health is influenced by various biological and social factors [2], including disorders of the functional state of the thyroid gland. In clinical practice, a large amount of data has been accumulated that thyroid hormone deficiency of any degree adversely affects the child's body, is a factor in a high risk of growth and development in children, the formation of chronic pathology and the growth of socially significant diseases. Against the background of iodine deficiency, there are disorders of neuropsychological development, which have a wide range - from a decrease in mild intelligence to severe forms of endemic cretinism. In a study on adults by Correira et al [11], HL was shown to cause more deterioration of cognitive functions as compared to overt hypothyroidism. There are very few studies investigating the cognitive functions in children and adolescents diagnosed with HL. In the study by Aijaz et al [12], attention deficit was found to be more frequent in children diagnosed with HL than in healthy controls. Wu et al [13] reported that adolescents with a diagnosis of HL showed lower performance in tests measuring cognitive functions as compared to adolescents with subclinical hyperthyroidism. Conflicting results were obtained in studies measuring the outcome of neurocognitive functions in hypothyroid patients who were diagnosed during screening studies and treated at an early phase. With the purpose of predicting the difficulties in the areas of active/passive attention and the selective attention of the children in the study, WISC-R Digit Sequences Subtest scores were evaluated, and it was observed that the children diagnosed with SH

obtained poor results in this subtest. The Stroop test demonstrates the ease of changing the perceptual organization according to the changing demands and under the influence of a "deteriorating effect", the capability of suppressing a habitual behavioral pattern and performing unordinary acts [14].

Our studies have revealed some changes in the cognitive performance of children with laboratory hypothyroidism. It can be predicted that in order to achieve high or medium success in school, all the compensatory capabilities of the body are involved, which is certainly a risk factor for the development of psycho-emotional and somatic disorders.

Chronic iodine deficiency in the environment is registered in many countries [15-18] and it causes serious threats for public health. In spite of serious outcomes IDD might have they can be quite successfully prevented, and there are not so many social and medical problems that can be solved such easily. Global efforts made by the world society have substantially changed geography of IDD prevalence; use of iodized salt in households has been recognized as a basic way to fight the above-mentioned morbid state. In relation to that, many countries have changed their national legislation related to regulation of population nutrition [19-21]. However, such a radical way hasn't been eventually supported by all the countries in the world, either due to moral and ethical reasons (freedom of choice), or economic and political ones.

Conclusion. Children with subclinical hypothyroidism are characterized by decreased memory, instability of attention and decreased ability to concentrate, impaired fine motor skills, which generally reduces their mental capacity.

The limitation of this study is the relative smallness of the sample.

References

1. van Trotsenburg P, Stoupa A, Léger J et al. Congenital Hypothyroidism: A 2020-2021 Consensus Guidelines Update-An ENDO-European Reference Network Initiative Endorsed by the European Society for Pediatric Endocrinology and the European Society for Endocrinology. Thyroid : official journal of the American Thyroid Association, 2021;3:387–419. https://doi.org/10.1089/thy.2020.0333.

2. Zimmermann MB, Jooste PL, Pandav CS. Iodine-deficiency disorders. Lancet. 2008;372:1251-1262.

3. Mohammed H, Marquis GS, Aboud F, Bougma K, Samuel A. TSH Mediated the Effect of Iodized Salt on Child Cognition in a Randomized Clinical Trial. Nutr Metab

Insights. 2021;14:11786388211025352. Published 2021 Jun 17. doi:10.1177/11786388211025352.

4. Aboud FE, Bougma K, Lemma T, Marquis GS. Evaluation of the effects of iodized salt on the mental development of preschool-aged children: a cluster randomized trial in northern Ethiopia. Matern Child Nutr. 2017;13:e12322.

5. Teti C, Panciroli M, Nazzari E et al. Iodoprophylaxis and thyroid autoimmunity: an update. Immunol Res. 2021;69(2):129-138. doi:10.1007/s12026-021-09192-6.

6. Yoo WS, Chung HK. Subclinical Hypothyroidism: Prevalence, Health Impact, and Treatment Landscape. Endocrinol Metab (Seoul). 2021;36(3):500-513. doi:10.3803/EnM.2021.1066.

7. Biondi B. Natural history, diagnosis and management of subclinical thyroid dysfunction. Best Pract. Res. Clin. Endocrinol. Metab. 2012;26:431–446. doi: 10.1016/j.beem.2011.12.004.

8. Bassett JH, Williams GR. Role of Thyroid Hormones in Skeletal Development and Bone Maintenance. Endocr Rev. 2016;37(2):135-187. doi:10.1210/er.2015-1106

9. Ergur AT, Taner Y, Ata E, Melek E, Bakar EE, Sancak T. Neurocognitive functions in children and adolescents with subclinical hypothyroidism. J. Clin. Res. Pediatr. Endocrinol. 2012;4:21–24. doi: 10.4274/Jcrpe.497.

10. Lynch S, Pfeiffer CM, Georgieff MK et al. Biomarkers of Nutrition for Development (BOND)-Iron Review. *J Nutr*. 2018;148(suppl_1):1001S-1067S. doi:10.1093/jn/nxx036.

11. Correira N, Mullally S, Cooke G et al. Evidence for a specific defect in hippocampal memory in overt subclinical hypothyroidism. J Clin Endocrinol Metab. 2009;94:3789–3797.

12. Aijaz NJ, Flaherty ME, Preston T, Bracken SS, Lane AH, Wilson TA. Neurocognitive function in children with compensated hypothyroidism: Lack of short term effects on or off thyroxine. BMC Endocr Disord 2006;6:2. 2006;6:2–2.

13. Wu T, Flowers JW, Tudiver F, Wilson JL, Punyasavatsut N. Subclinical thyroid disorders and cognitive performance among adolescents in the United States. BMC Pediatrics. 2006;19:6–12

14. Levie D, Korevaar TIM, Bath SC et al. Association of Maternal Iodine Status with Child IQ: A Meta-Analysis of Individual Participant Data. *J.* Clin. Endocrinol. Metab. 2019;104:5957–5967. doi: 10.1210/jc.2018-02559.

15. Korobitsyna R, Aksenov A, Sorokina T et al. Iodine Status of Women and Infants in Russia: A Systematic Review. Int J Environ Res Public Health. 2020;17(22):8346. doi:10.3390/ijerph17228346

16. Bath S.C. The effect of iodine deficiency during pregnancy on child development. Proc. Nutr. Soc. 2019;78:150–160. doi: 10.1017/S0029665118002835.

17. Melnichenko GA, Troshina EA, Platonova NM et al. Iodine deficiency thyroid disease in the Russian Federation: The current state of the problem. Analytical review of publications and data of official state statistics (Rosstat) Cons. Med. 2019;21:14–20. doi: 10.26442/20751753.2019.4.190337

18. Manousou S., Dahl L., Thuesen B.H., Hulthén L., Nyström H.F. Iodine deficiency and nutrition in Scandinavia. Minerva Med. 2016;108:147–158

19. Mokhort T.V., Kolomiets N.D., Petrenko S., Fedorenko E.V., Mokhort A. Dynamic monitoring of iodine sufficiency in Belarus: Results and problems. Probl. Endocrinol. 2018;64:170–179. doi: 10.14341/probl8686.

20. Phedorenko E, Kolomiets N, Mokhort T, Volchenko A, Mokhort E, Petrenko S, Sychik S. Risk communication as a component that provides stability of strategy aimed at eliminating diseases caused by iodine deficiency in Belarus. Health Risk Anal. 2019:58–67. doi: 10.21668/health.risk/2019.1.06.eng.

21. Abel MH, Caspersen IH, Sengpiel V et al. Insufficient maternal iodine intake is associated with subfecundity, reduced foetal growth, and adverse pregnancy outcomes in the Norwegian Mother, Father and Child Cohort Study. BMC Med. 2020;18:1–17. doi: 10.1186/s12916-020-01676-w.

Funding. The research was not granted any sponsor support.

Conflict of interests. The authors state there is no any conflict of interests.

This article is a fragment of the complex scientific research work of the Bukovinian State Medical University Ministry of Health of Ukraine (state registration number 0116U002937).