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The Assessment of Risk Factors for Development of Disability in Children with Congenital Hypothyroidism in Uzbekistan within a Neonatal Screening

Gulnara N. Rakhimova[1*], PhD, ScD; Gulshad M. Zhiemuratova[2]; Anna V. Aliyeva[3], PhD

[1]*Tashkent Institute of Postgraduate Medical Education, Tashkent, Uzbekistan*
[2]*Endocrinological dispensary of the Republic of Karakalpakstan, Nukus, Republic of Karakalpakstan, Uzbekistan*
[3]*Republican Specialized Scientific-Practical Medical Centre of Endocrinology named after Academician Ya. Kh. Turakulov, Tashkent, Uzbekistan*

Abstract

The aim of this study was to detect the most significant risk factors leading to disability in children with congenital hypothyroidism (CH) in the autonomous Republic of Karakalpakstan (RK) during neonatal screening (NS).

Methods and Results: We used data of patients with CH registered within NS in the RK in 1998-2019 by the Center for Screening of Mother and Child. To predict and calculate the most significant risk factors for disability in children with CH, we used the method of normalizing intensive indicators by E. Shigan, based on the Bayes theorem.

The study recruited 111 patients with CH aged from 2 months to 20 years. Among the patients, there were 79(71.2%) girls and 32(28.8%) boys. Additionally, 34(30.6%) children with CH had been disabled since childhood. The lack of compensation after the start of treatment had the highest and most significant degree of disability risk (RR=6.39, 95% CI: 7.4-1.2). Among patients diagnosed outside of screening, disability developed 4.1 times more often than with the results of NS (RR=4.0, 95% CI: 1.1-10.6). In CH patients diagnosed outside of screening, "absence of reagents" was a significant factor increasing the risk of disability by 6.1 times (RR=6.1, 95% CI: 1.8-11.2). Such risk factors as "home delivery" and "parental refusal of the primary test" increased the risk of disability by 3.4 times (RR=3.4, 95% CI: 2.5-8.4) and 1.6 times (RR=2.4, 95% CI: 2.93-7.12), respectively. The possible errors or false-negative answers in the "normal" secondary test and the "normal" primary test increased the risk of disability by 3.3 times (RR=4.0, 95% CI: 3.2-10.7) and 2.4 times (RR=2.42, 95% CI: 2.93-7.12), respectively. Factors such as the "late response to retesting" (RR=0.82 95% CI: 0.65-0.54), "late awareness on the part of the medical staff" (RR=0.29, 95% CI: 0.27- 0.08), and "parental refusal of treatment" (RR=1.03, 95% CI: 0.81-0.84) showed less significance in patients' disability. The "starting treatment after 1 month" factor was 4.2 times more likely to result in disability than "starting treatment before 1 month" (RR=4.2, 95% CI: 4.5 -1.1). Cancellation of levothyroxine by parents for children up to 3 years of age and cancellation of treatment by parents after 3 years more likely resulted in disability by 1.4 times (RR=1.43, 95% CI: 1.4 -2.01) and 3.3 times (RR=3.33, 95% CI: 3.3-10.9), respectively.

***Conclusion*:** the most significant risk factors for the development of disability in children with CH in the RK were (in descending order): no compensation after starting treatment, no reagents for screening, starting treatment after 1 year, diagnostics outside of screening, cancellation of L-T4 by parents before and after age 3 years, false-negative secondary TSH test, false-negative primary test, parents refusing the primary test, and childbirth at home.(**International Journal of Biomedicine. 2021;11(3):265-270.**)

Key Words: risk factors • congenital hypothyroidism • disability • neonatal screening

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Abbreviations

CH, congenital hypothyroidism; **CH-C**, congenital central hypothyroidism; **NII**, normalized intensive indicator; **NS**, neonatal screening; **THs**, thyroid hormones; **TSH**, thyroid stimulating hormone.

Introduction

Primary congenital hypothyroidism (CH) is a congenital deficiency of thyroid hormones (THs) in newborns, resulting from incomplete development of the thyroid gland in ontogenesis or from disorder of synthesis and secretion of thyroid hormones, which leads to a lag in the development of all organs and systems of the body, and especially to severe mental retardation and delayed physical development.[1-4] THs are essential for normal growth and development of the central nervous system, especially in the first 3 years of life.[5] During the period of rapid growth and active neurogenesis, the brain becomes especially sensitive to deficiency of thyroxine. Therefore, thyroid failure delays the development of the brain and its maturation, leading to irreversible mental retardation.[1]

The prevalence of CH varies significantly in different countries of the world and ranges from 1 to 2000 to 1 to 3000 newborns. The incidence of CH varies significantly among different ethnic groups and geographic locations, depends on the severity of iodine deficiency in the country, and occurs 2-2.5 times more often in girls than in boys.[1,6-8]

In the mid-70s, many developed countries introduced the state system of NS for CH because of a high incidence of CH, as well as serious consequences and late diagnosis. (9,10) Mass screening was first carried out in Canada in 1974, and today this method is used in the majority of developed countries.[11]

The organization of NS for CH in Uzbekistan is carried out in accordance with the Resolution of the Cabinet of Ministers of the Republic of Uzbekistan, dated 01.04.1998, "On the creation of the State system for early detection of congenital and other pathologies in newborns and pregnant women to prevent the birth of disabled people." A modern screening center was organized in the autonomous Republic of Karakalpakstan (RK) in 1997.[12] Modern screening centers are organized in each region. Diagnostics, treatment, and monitoring of patients with CH aged up to 18 years is carried out free of charge under the supervision of screening centers.

Among the studied risk factors affecting mental and physical development, the most important are: 1) the first therapeutic dose, 2) the age treatment is initiated, 3) the age thyroxine levels are normalized.[13] The latest Guidelines of the European Society for Pediatric Endocrinilogy 2020-2021 confirm that after a newborn receives a positive result of screening for CH, immediate administration of levothyroxine in the first 2 weeks at a dose of 10-15 μg/kg per day is the most optimal.[8]

Despite the development of more accurate test programs, approximately 5% of cases of CH can still be missed in any screening program. Causes may be loss of sample collection, poor samples, misinterpretation of results, subclinical hypothyroidism, or, if TSH is measured alone, failure to detect infants with CH-C.[14]

Any screening system turns into large financial costs for the state. For this reason, any screening system requires periodic evaluation of its effectiveness. In the RK, among 111 patients with CH, 34 are disabled. Therefore, it became necessary to assess the effectiveness of NS in the RK. There were no similar studies in Uzbekistan.

The aim of this study was to detect the most significant risk factors leading to disability in children with CH in the RK during NS.

Materials and Methods

We used data of patients with CH registered within NS in the RK in 1998-2019 by the Center for Screening of Mother and Child. The results of NS for CH were evaluated according to the level of TSH in capillary blood, collected on filter paper from newborns 4-5 days after birth. Testing for THs (TSH, total T4, and total T3) was carried out in the NS laboratory using the DELFIA multifunctional automated immunological laboratory, consisting of a Wallas VICTOR-2D analyzer and a set of auxiliary equipment.

The time for prescribing treatment after birth, the thyroxine dose, and the achievement of the target TSH levels were assessed on the basis of the ESPE recommendations.[3]

To predict and calculate the most significant risk factors for disability in children with CH, we used the method of normalizing intensive indicators by E. Shigan, based on the Bayes theorem.[15]

Based on the literature data, the following risk factors were identified and were included in the analysis: the time of diagnosis during screening, diagnostics outside the screening, the timing treatment was initiated (up to 1 month or after 1 month), compensation after the start of treatment, correctly selected dosage of levothyroxine directly at diagnosis, refusal of treatment by parents, lack of reagents for screening, parents' refusal of primary testing, the rate of "normal" primary test, the rate of "normal" retest, late informing of parents about retesting by medical personnel, late parental response to retesting, childbirth at home, and cancellation of treatment by parents (under age 3 and over age 3).

The NII was calculated for the gradation of each factor, that is, the frequency of cases of disability, according to this gradation, was divided by the total frequency of disability in the surveyed population (30.6%). In order to determine how many times the presence of a factor increases the risk of developing disability, the relative risk index (RR) was calculated. The indicators of RR were also determined according to the gradation of each factor. After determining the NII and RR, for a comprehensive assessment of the phenomenon under study, the corresponding NII values were multiplied by the RR indicators. That is, the integral assessment was determined by the formula: $X = NII \times RR$, where X is the integral risk assessment.

Statistical analysis was performed using Microsoft Excel software package. The normality of distribution of continuous variables was tested by one-sample Kolmogorov-Smirnov test. Baseline characteristics were summarized as frequencies and percentages for categorical variables and as mean±standard deviation (SD) for continuous variables. For data with normal distribution, inter-group comparisons were performed using Student's t-test. A probability value of $P<0.05$ was considered statistically significant.

Results

The study recruited 111 patients with CH aged from 2 months to 20 years. Among the patients, there were 79(71.2%) girls and 32(28.8%) boys. Additionally, 34(30.6%) children with CH had been disabled since childhood, of which 6(17.6%) had a normal TSH level at Stages 1-2 of screening (the so-called "missed" results), 18(52.9%) children were identified outside of screening, and 10(29.5%) during the screening.

During NS of 87 newborns, disability since childhood was diagnosed in 16(18.4%) of patients. Among 24 children outside NS, disability since childhood was diagnosed in 18(75%). Several factors have been identified that affect the CH diagnosis (Table 1).

Table 1.

Frequency of some risk factors in children with CH and disability

	n	Disability	
		n=34	%
Frequency of disability within NS	87	16	18.4
Frequency of disability outside NS	24	18	75
Risk factors for CH during NS			
	N	n =13	%
Late response to retesting	15	4	26.7
Late awareness on the part of the medical staff	18	2	11.1
"normal" primary test	9	6	66.7
"normal" secondary test	1	1	100
Risk factors for disability and late diagnosis of CH (outside NS)			
	N	n =18	%
Home delivery	2	2	100
Absence of reagents	20	15	75
Parental refusal of the primary test	2	1	50
Risk factors for disability depending on treatment			
	N	n = 8	%
Early onset of treatment (within 1 month)	40	4	10
Compensation after the onset of treatment	18	1	5.6
Decompensation after the onset of treatment	22	3	35.5
Early onset of treatment (within 1 month)			
	N	n =4	%
Cancellation of treatment by parents (before age of 3 years)	7	3	42.9
Cancellation of treatment by parents (after age 3 years)	1	1	100

During the neonatal period, additional risk factors were identified in CH children, affecting treatment and leading to the disability (Table 1). Among patients diagnosed outside of screening, disability developed 4.1 times more often than with the results of NS (RR=4.0, 95% CI: 1.1-10.6). In CH patients diagnosed outside of screening, "absence of reagents" was a significant factor increasing the risk of disability by 6.1 times (RR=6.1, 95% CI: 1.8-11.2). Such risk factors as "home delivery" and "parental refusal of the primary test" increased the risk of disability by 3.4 times (RR=3.4, 95% CI: 2.5-8.4) and 1.6 times (RR=2.4, 95% CI: 2.93-7.12), respectively.

The possible errors or false-negative answers in the "normal" secondary test and the "normal" primary test increased the risk of disability by 3.3 times (RR=4.0, 95% CI: 3.2-10.7) and 2.4 times (RR=2.42, 95% CI: 2.93-7.12), respectively. Factors such as the "late response to retesting" (RR=0.82 95% CI: 0.65-0.54), "late awareness on the part of the medical staff" (RR=0.29, 95% CI: 0.27- 0.08), and "parental refusal of treatment" (RR=1.03, 95% CI: 0.81-0.84) showed less significance in patients' disability (Table 2).

The "starting treatment after 1 month" factor was 4.2 times more likely to result in disability than "starting treatment before 1 month" (RR=4.2, 95% CI: 4.5 -1.1). Cancellation of levothyroxine by parents for children up to 3 years of age and cancellation of treatment by parents after 3 years more likely resulted in disability by 1.4 times (RR=1.43, 95% CI: 1.4 -2.01) and 3.3 times (RR=3.33, 95% CI: 3.3-10.9), respectively. The lack of compensation after the start of treatment had the highest and most significant degree of disability risk (RR=6.39, 95% CI: 7.4-1.2) (Fig.1).

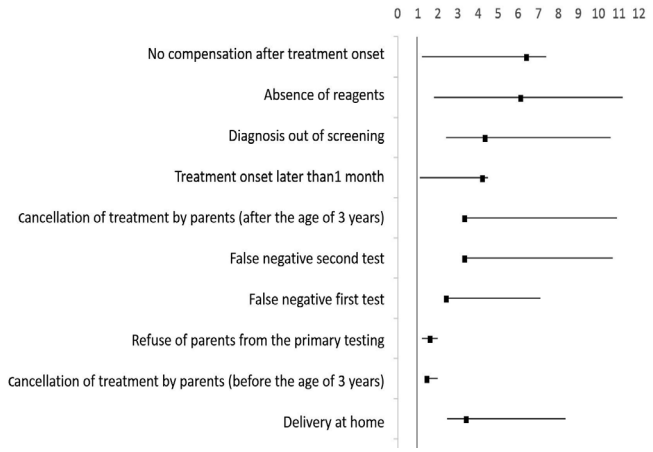

Fig.1. *The most significant risk factors for the development of disability among children with CH*

When assessing thyroid function, out of 40 patients with an early start of treatment with levothyroxine, only 18(45%) children were compensated and 22(55%) patients were decompensated (TSH>5μU/ml). The data obtained confirm that a significant proportion of patients with CH were decompensated (Table 3).

Table 2.

Integral analysis of risk factors for the development of disability among children with CH

Risk factor	Gradation of factors	Disability, %	NII	RR	X
Decompensation after the onset of treatment	No	5.555556	0.1815541	6.4	1.1596036
	Yes	35.483871	1.1596036		7.4065006
Absence of reagents	Yes	75	1.8382353	6.1	11.226366
	No	12.280702	0.3009976		1.8382353
Diagnosis	NS	18.441379	0.5634438	4.0	2.4397115
	Out of NS	75	2.4509804		10.612745
Onset of treatment	Within 1 month	10	0.3267974	4.2	1.0686275
	Later	42.253521	1.380834		4.5153273
Cancellation of treatment by parents (after age 3 years)	Yes	100	3.2679739	3.3	10.893246
	No	30	0.9803922		3.2679739
"normal" secondary test	Yes	100	3.2679739	3.3	10.686275
	No	30	0.9803922		3.2058824
"normal" primary test	Yes	66.666667	2.1786492	2.4	7.124183
	No	27.45098	0.8970909		2.9334871
Parental refusal of the primary test	Yes	50	1.2254902	1.6	1.9980818
	No	30.666667	0.751634		1.2254902
Cancellation of treatment by parents (before age 3 years)	Yes	42.857143	1.4005602	1.4	2.0137087
	No	29.807692	0.9741076		1.4005602
Factors of late onset of treatment (40.8%)					
Home delivery	Yes	100	2.4509804	3.4	8.355615
	No	29.333333	0.7189542		2.4509804
Parental refusal of treatment	Yes	33.333333	0.8169935	1.0	0.8417508
	No	32.352941	0.7929642		0.8169935
Late response to retesting	Yes	26.666667	0.6535948	1.2	0.79064
	No	32.258065	0.7906388		0.95642
No assessment of thyroid function after age 3 years	Yes	25	0.6127451	1.3	0.83241
	Assessed	33.962264	0.8324084		1.13082
No assessment of thyroid function before age 3 years	Yes	14.285714	0.3501401	2.3	0.80532
	Assessed	32.857143	0.8053221		1.85224
No timely ultrasound	Yes	15	0.3676471	2.5	0.90299
	Done	36.842105	0.9029928		2.21788
Late awareness on the part of the medical staff	Yes	11.111111	0.2723312	3.4	0.91392
	No	37.288136	0.9139249		3.06707

Table 3.

TSH level and thyroxine dose depending on the achievement of compensation in children with starting treatment before 1 month

	Compensation after the onset of treatment (n=18)	Decompensation after the onset of treatment (n=22)	*P*-value
TSH before treatment, μU/ml	150.9±44.2	200.5 ±37.5	<0.05
TSH after treatment onset, μU/ml	1.6±0.4	47.9±12.1	<0.05
Levothyroxine dose, μg/day	35 ±3.1	29.3±2.0	>0.05
Levothyroxine dose, μg/kg/day	9.3±0.9	7.3±0.4	<0.05

In patients with congenital hypothyroidism in a state of compensation, the TSH level after the start of treatment was 1.6±0.4 μU/ml vs. 47.9±12.1 μU/ml in decompensation state (P<0.05). In patients with compensation, the prescribed dose of levothyroxine was 9.3±0.9 μg/kg vs. 7.3±0.4 μg/kg in patients with decompensation (P<0.05). It should be noted that in most newborns with congenital hypothyroidism, the prescribed doses of levothyroxine were significantly lower than those recommended by ESPE.[9] In addition, in the first months of life, compensation was assessed based on the total level of T4 only in 22.5% of cases. The lack of compensation after the start of treatment increased the risk of disability in children with congenital hypothyroidism by 6.4 times.

Discussion

In Uzbekistan, according to the results of screening from 1998 to 2017, 5,820,457 newborns were tested, and congenital hypothyroidism was diagnosed in 2323 cases.[16] In the Republic of Karakalpakstan for the period from 2003 to 2019, 383,018 newborns were examined and 124 patients were diagnosed with congenital hypothyroidism. In 2003-2019, the population frequency of congenital hypothyroidism in the Republic of Karakalpakstan, according to the results of neonatal screening, was 1:3089 newborns. Of the children with congenital hypothyroidism, 8(9.9%) were referred to the supervision of an endocrinological dispensary, 1.2%of parents refused treatment, 4(4.9%) moved, and 3 children died (3.7%).[17]

Our study found that girls are more likely than boys to have a congenital hypothyroidism, with a ratio of 2.5:1. According to research by Yang et al.,[18] congenital hypothyroidism was also more prevalent in girls than in boys, but the reason is still unclear.[19]

We identified repeated cases of congenital hypothyroidism in 2 families (3.6%), which coincides with the literature data. According to I.I. Dedov,[1] 85% of congenital hypothyroidism cases are sporadic, and the remaining 15% of cases are caused by dyshormonogenesis.

In the Republic of Karakalpakstan from 2003 to 2019, the annual neonatal screening for congenital hypothyroidismwas an average of 60.6%. The lack of full screening coverage

was mainly due to irregular laboratory testing. For example, due to the lack of reagents, screening was not carried out in 2004 for 1 year. During this period of time, the pediatric endocrinologists and neuropathologists annually diagnosed 2-3 cases of congenital hypothyroidism based on the typical symptoms of the disease. The absence of reagents increased the risk of patients with congenital hypothyroidism developing a disability by 6.1 times, which is consistent with a study by Alimova et al.[20]

Thus, within neonatal screening, 78 patients were diagnosed with congenital hypothyroidism, and in 9 patients the diagnosis of congenital hypothyroidism was not confirmed in Stage 1, due to the low TSH levels, but the clinical signs appeared later together with high TSH levels. Thus, during the screening, 10.3% of children were missed; this is somewhat higher than in a study by A. Büyükgebiz,[14] who found that 5% of children with congenital hypothyroidism might still be missed in any screening program.

During the screening, it was revealed that the time needed to make the diagnosis and prescribe treatment in 78 newborns with congenital hypothyroidism was 1.5 months, on average 46.2±12.4 days after birth with fluctuations from 10 to 207 days, although according to the ESPE recommendations, testing should be done within 2 weeks.[9] This discrepancy is explained by the large distances in the RK between populated areas, cities, and regional centers, so it takes more time to deliver blood samples from maternity hospitals to the screening center. It is proposed to solve these problems by allocating financing to maternity hospitals for postage. Similar problems were identified in a study by Kasatkina et al.[16]

Multivariate analysis confirmed that neonatal screening for congenital hypothyroidism is effective. Outside of screening, disability for congenital hypothyroidism was 4 times higher than during screening. It is necessary to strive for an early start of treatment in the first month of life and use the dose of levothyroxine according to the level of free or total T4 until TSH normalizes. The prescribed first doses of levothyroxine should correspond to international recommendations - 10-15 μg/kg of body weight.

Thus, the most significant risk factors for the development of disability in children with congenital hypothyroidism in the Republic of Karakalpakstan were (in descending order): no compensation after starting treatment, no reagents for screening, starting treatment after 1 year, diagnostics outside of screening, cancellation of L-T4 by parents before and after age 3 years, false-negative secondary TSH test, false-negative primary test, parents refusing the primary test, and childbirth at home.

Competing Interests

The authors declare that they have no competing interests.

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***Corresponding author:** Prof. Gulnara N. Rakhimova, the Head of the Department of Endocrinology, Tashkent Institute of Postgraduate Medical Education, Tashkent, Uzbekistan. E-mail: diabetgulnora@hotmail.com.*

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