Original Paper

A Cross-Sectional Study to Assess Thyroid Function in Infants and Children in a City from South-Western Romania

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ABSTRACT: Thyroid hormones are critical regulators of growth, myelination of the nervous system, metabolism, and organ function. The most prevalent endocrinopathies in childhood are related to thyroid disorders. Thyroid problems in children and adolescents have a significantly different etiology and clinical presentation than in adults. Thus, pediatric medical care involves an understanding of the unique features of thyroid function and dysfunction during childhood and adolescence. The etiology and clinical manifestations of thyroid disorders in children and adolescents are vastly different from those in adults. The particular aspects of thyroid function and malfunction in childhood and adolescence are hence part of pediatric medical therapy. To prevent persistent nervous system damage and developmental problems, it is vital to recognize and treat thyroid dysfunction in neonates as early as possible. The purpose of the research was to understand more how children's thyroid problems function, structure, and prevalence. The research examined 30 children under the age of 16 years who had symptoms that were linked to thyroid problems. In addition to demographic and family information, thyroid ultrasounds and blood samples for the detection of T3, T4, and TSH were obtained. Females surpassed males by a small majority (2.33:1 ratio).Out of the total children included in the study, 14(46.7%) cases for autoimmune thyroiditis, 2(6.67%) cases for congenital hypothyroidism, 1(3.33%) case for hyperthyroidism, 1(3.33%) case for hyperthyroidism-Graves disease, 8(26.7%) cases for hypothyroidism and 4(13.3%) cases for subclinical hypothyroidism.

KEYWORDS: *Thyroid disorders, children, hyperthyroidism, hypothyroidism.*

Introduction

Since the thyroid hormone economy changes dramatically around birth and throughout the first few years of life, it's important to early diagnose and treat endocrine gland problems.

The drastic long-term effects of untreated congenital hypothyroidism (CH) that occur due to delayed diagnosis underline the significance of routine screening for irregular thyroid function tests in newborns [1].

While congenital hyperthyroidism is rare and with a limited course, congenital hypothyroidism can have serious consequences, including heart failure, and can even be fatal to babies and young children who suffer from the disorder.

Even more tragic, congenital hypothyroidism has been confirmed to result in hyperthyroidism and various developmental issues in fetuses and newborns, and such complications can continue to surface in later life [2].

It should be taken into consideration that neonatal TSH increases within the first few hours of life and is followed by a peak in plasma T4 24 hours later.

Since an isolated measurement of TSH during the first 24 hours of life could result in the misdiagnosis of primary hypothyroidism, whereas an isolated measurement of T4 taken two days after birth will contribute to the misdiagnosis of hyperthyroidism, isolated measurement of TSH in the first 24 hours of life might be incorrect.

Even though the normal ranges of free T4 and total T3 cover a wider range in children than in adults, it is nevertheless crucial to note that key measures of thyroid function, such as the normal ranges of free T4 and total T3, extend to

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considerably higher levels in children than in adults.

Of the total number of problems that present, the majority are caused by an imbalance in thyroid hormone levels, but structural thyroid issues may also occur in infancy [3].

Thyroid diseases are frequently more prevalent in hypothyroidism than hyperthyroidism.

Hypothyroidism may be congenital, acquired during childhood or adolescence, manifest with or without symptoms, or develop slowly or suddenly.

In neonates, hypothyroidism is a major health condition that is discovered through newborn screening programs.

Hypothyroidism symptoms can be enigmatic, manifesting only in retrospect.

Cold sensitivity, bradycardia, carotenemia, coarse, brittle hair, dry skin, pallor, and myxedema are some of the manifestations that can occur.

Because these signs and symptoms might be subtle, long-term hypothyroidism can go unnoticed for years.

The main cause of hypothyroidism in children is Autoimmune thyroiditis [4,5].

When chronically present, autoimmune thyroiditis also results in juvenile acquired hypothyroidism, which can manifest as growth failure [6].

In infants, hypothyroidism may be caused by iodine deficiency or hypothalamic-pituitary dysfunction.

One of the most prevalent signs and symptoms of thyroid disease in children is a swollen thyroid gland caused by autoimmune thyroiditis.

Anti-thyroglobulin and anti-thyroperoxidase antibodies are associated with it, and it is described by lymphocytic infiltration of the thyroid gland, leading to thyromegaly [7,8].

Hashimoto syndrome can be associated with euthyroidism, hypothyroidism, or intermittent hyperthyroidism, depending on the presence of the antithyroid antibodies [7,8].

Thyroid gland damage is caused by both antibody-mediated and cell-mediated mechanisms Hashimoto thyroiditis is rare in very early newborns [9], but generally develops in adolescents, with girls more likely to be affected than boys [7].

Typically, the thyroid gland is diffusely swollen and palpation can reveal an irregular, cobblestone texture.

Asymmetric thyroid enlargement can be observed, resembling a thyroid nodule.

Antithyroid antibodies in the absence of lesions on ultrasound may assist in distinguishing inflammation from other pathological changes.

Subclinical hypothyroidism is defined by normal T4 and T3 levels but an abnormally increased TSH level [10,11].

As described earlier, many infants are misdiagnosed with this condition when their TSH levels are found to be over the adult reference range.

But, if pediatric-based TSH values would be used, the majority of children diagnosed with hypothyroidism would be normal.

As a result, several researchers have questioned whether teenagers suffer of subclinical hypothyroidism [10,11].

In children, hyperthyroidism is less common than hypothyroidism, although it is substantially more symptomatic.

The main cause of thyrotoxicosis in children is Graves disease.

It is described by diffuse goiter, hyperthyroidism, and, in limited circumstances, ophthalmopathy.

Additionally, autonomously functioning thyroid nodules, neonatal thyrotoxicosis, and thyroid infections can cause hyperthyroidism in infants.

Diagnostic imaging of the thyroid is an important aspect of the process.

Ultrasound is recommended as the initial diagnostic test in all children with thyroid disorders due to its non-invasive nature, low cost, and high sensitivity.

The size and location of the thyroid, as well as its ultrasound characteristics, including composition (solid, cystic proportion, or spongiform), echogenicity (hyper-, iso-, hypoechoic), margins (smooth, irregular, lobulated, ill-defined, Halo, extrathyroid extension), existence and type of calcifications, form, if taller than wide, and vascularity, should all be included in the US report [12].

Aim

The purpose of our study was to assess thyroid function and structure in order to establish a diagnosis based on the collected data and to analyze the average age at diagnosis, the frequency according to sex and age group.

Material and Methods

Patients Data

The study was performed at the Pediatric Clinic of the Emergency County Hospital of Craiova on a number of 30 patients, diagnosed with thyroid disorders between 2018 and 2020, all of them under the age of 18.

This study was approved by the Ethics Committee of the University of Medicine and Pharmacy of Craiova (No.6/20.01.2021) and carried out under the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

All experiments were performed under relevant guidelines and regulations.

Approval was obtained from the institutional review boards of all institutions, and the requirement for informed consent was obtained as the study design was based on prospective research of medical tests and ultrasound images.

TPOAb and/or TGAb were found to be positive in the majority of cases.

On thyroid ultrasound, the most of patients had morphological alterations, as well as irregular thyroid function or an increased thyroid gland.

Pediatric endocrinologists recommended patients for assessment when they had one or more of the following symptoms: increased thyroid antibodies, goiter, or other symptoms associated to thyroid dysfunction.

The diagnosis was established using ultrasound findings and multiple laboratory tests.

To describe the thyroid gland, endocrinologists and pediatricians used a low-medium-resolution (7.5 MHz) ultrasound instrument (Siemens SonoAce) fitted with a linear transducer.

The thyroid volume, ultrasound pattern, heterogeneity, number and size of nodules and presence of pseudo-nodules and cysts were all determined by ultrasound.

The patient is generally relaxed throughout the procedure, which will only last only a few minutes unless the lateral neck needs to be evaluated, and does not require the patient to discontinue any medications.

The assessments are typically performed with the patient reclining with his or her neck hyperextended, but it can also be accomplished when the patient is seated.

Thyroid function was evaluated using a variety of laboratory tests, including TSH (thyroid stimulating hormone), free T4 (thyroxine), thyroid peroxidase and thyroglobulin antibodies, blood glucose levels, calcium, liver function, and vitamin D dosage.

For patients with hyperthyroidism, additional doses of Thyrotropin Receptor Antibodies (TRAb) were indicated.

Correlations were made between the findings and clinical data taken from patient histories.

Subgroups

Patients were divided into five subgroups based on their TSH level and FT4 level at admission: hyperthyroidism (TSH<0.03mIU/L and FT4>20pmol/L); euthyroidism with autoimmune thyroiditis (TSH 0.4-4.2mIU/L and FT4 10-20pmol/L; higher levels of TPOAb and TGAb); subclinical hypothyroidism (TSH 4.3-10-mIU/L and normal FT4); hypothyroidism (TSH>4.2mIU/L and FT4<10pmol/L); congenital hypothyroidism (TSH>20mIU/L and FT4<10pmol/L).

Statistical Analysis

Statistical analysis was realized using R statistical software [13].

The diagnosis groups were compared by the Kruskal-Wallis test for continuous variables [14].

Wilcoxon two-sample tests with Bonferroni correction have been used to establish pairwise comparisons for continuous variables.

The criteria for significance was defined at $p<0.05$.

Results

The study population included 30 participants (female-to-male ratio of 2.33:1) with a mean age of 10.6±4.31 years (range 0.04-16 years).

Mean TSH at presentation was 10.56±24.32mIU/L (range 0.03-101) and FT4 19.82±25.24pmol/L (range 5.21-121).

Mean TPOAb (UI/mL) was 97.30±116.84 (range 10-600) and mean TGAb (UI/mL) was 51.69±58.39 (range 10-336).

FT4 was below the normal value for 33% of patients and elevated for 6.67%.

TGAb was elevated for 23.3% of cases and TPOAb was elevated for 70% of cases.

Mean 1,25-(OH)2-Vitamin D3 (ng/ml) was 27.3±6.64 (range 16.2-43).

Mean Glucose level (mg/dl) was 91.93±22.44 (range 55-170).

Mean ALT (U/L) was 32.4±32.58 (range 13-176).

Mean AST (U/L) was 31.76±21.30 (range 10-101).

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Table 1. Clinical and biochemical results.

Diagnosis	Autoimmune thyroiditis	Congenital hypo-thyroidism	Hyper-thyroidism	Hyper-thyroidism-Graves disease	Hypo-thyroidism	Subclinical hypo-thyroidism	p-value
No Patients	14 (46.7%)	2 (6.67%)	1 (3.33%)	1 (3.33%)	8 (26.7%)	4 (13.3%)	
Gender (F:M) % male	11:3 (21.4%)	1:1 (50%)	0:1 (100%)	0:1 (100%)	6:2 (25%)	3:1 (25%)	
Age (Years)	11.7±3.35 (5-16)	0.055±0.02 (0.04-0.07)	14.8	15	10.4±3.24 (4.16-15)	10.1±3.73 (6-13.6)	0.1062 (not significant)
TSH (mIU/L)	2.44±0.683 (1.58-3.96)	99.5±2.12 (98-101)	0.05	0.03	6.91±1.33 (4.77-8.99)	7.16±1.88 (4.66-9.15)	0.0001945
FT4 (pmol/L)	16.8±2.10 (13.4-21.3)	7.78±1.51 (6.71-8.85)	100	121	7.55±1.73 (5.21-10.2)	15.6±3.88 (12.5-21.3)	0.0004976
TPOAb (U/mL)	108±53.9 (51.6-231)	46.9±10 (39.8-54)	600	301	45±31.7 (13.6-102)	31.1±2.97 (10-16.6)	0.001474
TGAb (U/mL)	72.4±80.2 (10-336)	38.0±21.3 (23-53.1)	40	50	32.2±18.7 (19.2-76)	28.4±15.1 (20-51)	0.19 (not significant)

In Table 1 are summarized the clinical and biochemical results.

The number of patients for each diagnosis: 14 (46.7%) cases for autoimmune thyroiditis, 2 (6.67%) cases for congenital hypothyroidism, 1 (3.33%) case for hyperthyroidism, 1 (3.33%) case for hyperthyroidism-Graves disease, 8 (26.7%) cases for hypothyroidism and 4 (13.3%) cases for subclinical hypothyroidism.

The proportion of female and male for each diagnosis: the ratio between female and male was 11:3 for autoimmune thyroiditis, 1:1 for congenital hypothyroidism, 0:1 for hyperthyroidism, 0:1 for Graves disease, 6:2 for hypothyroidism, and 3:1 for subclinical hypothyroidism.

The means and standard deviation, respectively the minimum and maximum values for each biochemical parameter: for Autoimmune thyroiditis, the mean of TSH was 2.44±0.683 with a range between 1.58 and 3.96; for Congenital hypothyroidism, the mean of TSH was 99.5±2.12 with a range between 98 and 101; for Hypothyroidism, the mean of TSH was 6.91±1.33 with a range between 4.77 and 8.99; for Subclinical hypothyroidism, the mean of TSH was 7.16±1.88 with a range between 4.66 and 9.15.

TSH levels were elevated (p=0.0022) in Hypothyroidism cases compared to those with Autoimmune thyroiditis.

In addition, FT4 levels were substantially lower (p=0.00009) in Hypothyroidism subjects compared to Autoimmune thyroiditis cases.

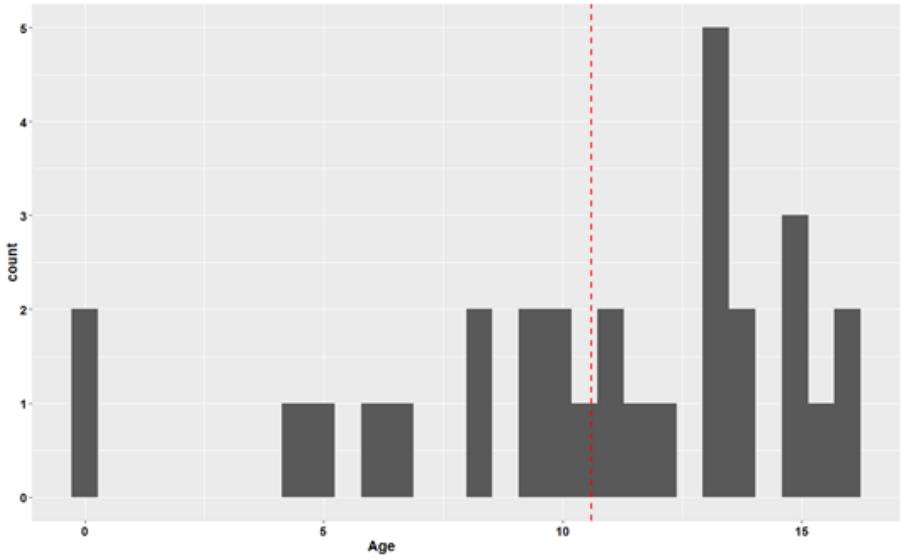

Figure 1. Age distribution among patients.

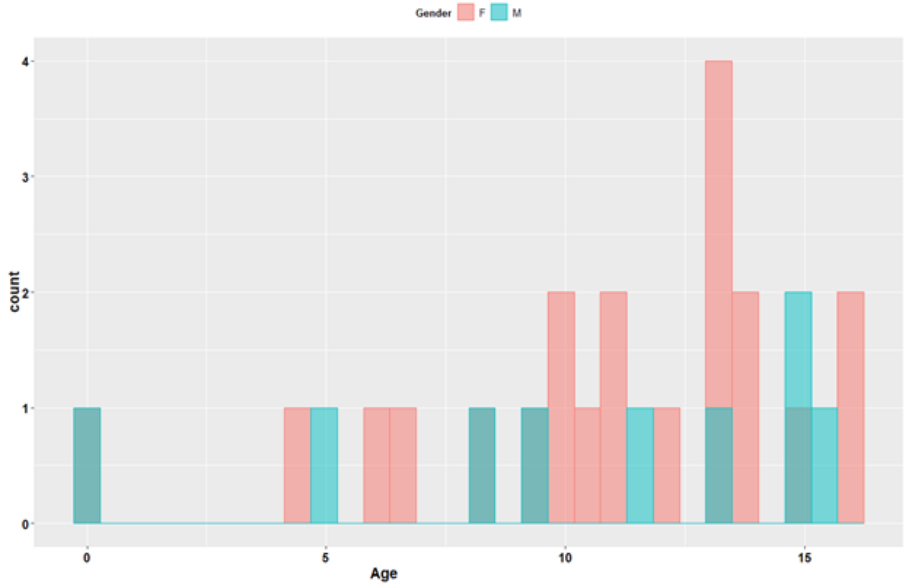

Figure 2. Age distribution among gender of patients.

The most common age group affected with Thyroid disorders was 10-16 years (Figure 1).

As illustrated in the image above, our patients had a slight female predominance (2.33:1 ratio) (Figure 2).

In Figure 3, Figure 4, Figure 5, and Figure 6, we can see the distribution of TSH, FT4, TPOAb, and TGAb.

The rectangle represents the middle 50% of the data, the line represents the median, and the whiskers indicate the extent of the data.

Outside the whiskers, the points had abnormal values.

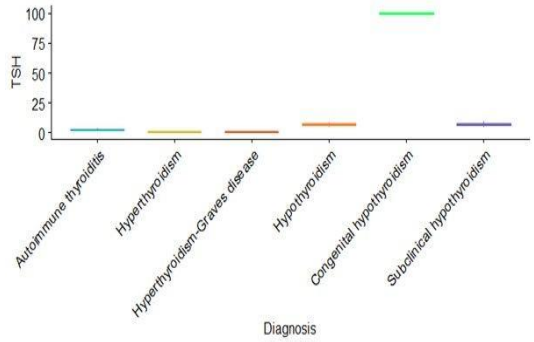

Figure 3. Distribution of TSH values according to each diagnosis.

The most elevated TSH values were reported at patients with Congenital hypothyroidism, while the lowest levels were noticed in patients with Hyperthyroidism and Hyperthyroidism.

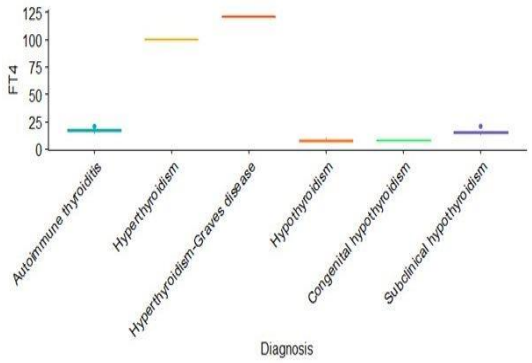

Figure 4. Distribution of FT4 values according to each diagnosis.

The highest value of FT4 was noticed in patients with Hyperthyroidism, especially the ones with Graves' disease, while the lowest were at patients with Hypothyroidism and Congenital hypothyroidism.

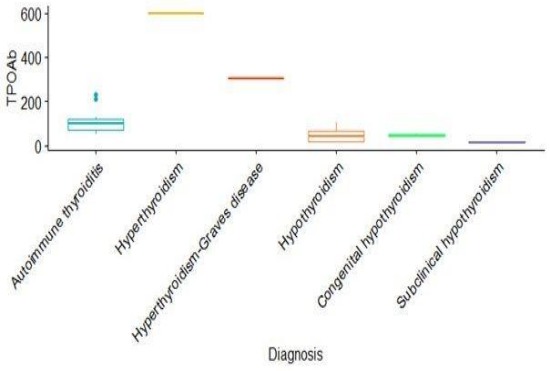

Figure 5. Distribution of TPOAb values according to each diagnosis.

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Normal values of TPOAb were noticed in Hypothyroidism, Congenital hypothyroidism and subclinical hypothyroidism, while abnormal values (elevated) were at patients with Autoimmune thyroiditis and Hyperthyroidism, including Graves disease.

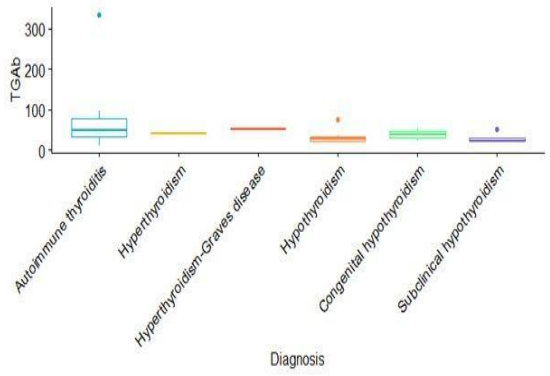


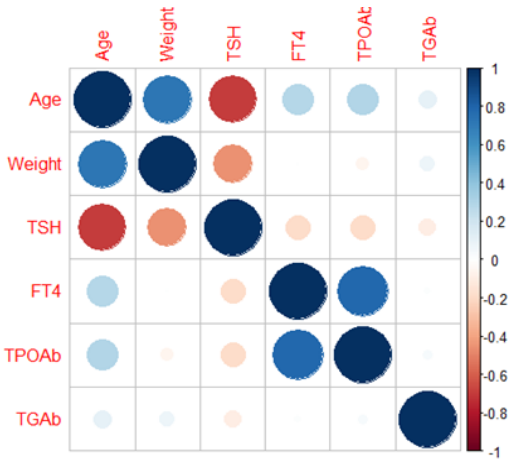
Figure 6. Distribution of TGAb values according to each diagnosis.

Most cases with abnormal TGAb were noticed at patients with Autoimmune thyroiditis, even the most elevated value.

Taking into account the matrix of correlations, strong correlations were between FT4 value and TPOAb (r=0.788, p=0.0000002), between age and TSH(r=0.69, p=0.000023), also between age and weight (r=0.72, p=0.000005), but we also observed a negative correlation between weight and FT4 value(r=0.002, p=0.09909543), FT4 value and TGAb (r=0.023, p=0.094313272) (Figure 7).

Mild correlations were between weight and TSH value (r=0.45, p=0.00115834).

Figure 7. The matrix of correlations, calculated for each pair of variables and the p-values corresponding to the significance levels of correlations.



Discussions

As part of our research, we evaluated the clinical and laboratory aspects of thyroid problems in children and adolescents, as well as their natural course.

We found that about 46.67% of the cases were diagnosed with Autoimmune thyroiditis, whereas only 3.33% of the cases were diagnosed with Congenital Hypothyroidism.

Thyroid diseases are more prevalent in female patients than in male patients, with a female to male ratio of 2.33:1 reported.

A similar result was obtained by Yelluri in his investigation, where he observed a 2:1 ratio [15].

Other similar studies conducted by Kapil et al (2.9:1), Hunter et al (2.8:1), and Shah et al (3:1) found a similar prevalence of females over males [16,17,18].

The most prevalent age group afflicted was 10-16 years, representing 63.33% of children, with a significant female gender predominance.

Onyeruika observed a comparable prevalence of a higher age group, where the mean age group was 11.2 years [19].

According to G Bala Bhaskara Reddy's study, the prevalence is higher in the age group 1-3 years, at 33.1% [20].

Even earlier, in 1979, Laditan found that the average age group of affected children was 5.4 years [21].

The most frequent cause for referral to our service was thyroid function deficiency or increased autoantibodies (70%) and the most common complaint were the abnormal values of TSH and FT4 (53.33%).

Serum TSH levels between 4.77 and 9.15mIU/L are suggestive for hypothyroidism, as well as low FT4 levels.

Female gender and an initial TSH level more than 6mIU/L were significant predictors of persistently increased TSH.

However, in this investigation, the cohort was not restricted to participants with AIT.

Congenital hypothyroidism was detected in two cases of this research, representing approximately 16.67%.

Various studies, however, have revealed an elevated frequency of congenital hypothyroidism.

Oyenusi et al. [22] reported a 46.7% prevalence of congenital hypothyroidism in their Nigerian study.

Congenital hypothyroidism was confirmed in the youngest patient, a 17-day-old boy.

In the current study, two children under the age of one month were diagnosed with congenital hypothyroidism.

According to Oyenusi et al., the youngest patient was 7 hours old [22].

Only 6.67% of the patients in this research developed hyperthyroidism.

This was supported by Singh et al., who reported a 6.1% incidence [23].

Conclusions

It is essential to detect thyroid issues early in order to improve children's development and growth.

Therefore, it is essential to understand risk factors, clinical manifestations, laboratory findings, and how to make an accurate diagnosis.

Additionally, parents are urged to recognize any anomalies in their children and seek quick medical attention, as thyroid issues require extensive care and support.

In summary, this study indicates that the most common disorder in this cohort group is Autoimmune thyroiditis with a percentage of 46.67.

Early detection is extremely important as the consequences of thyroid disease may affect the entire body.

Regardless of the successful outcome, follow-up investigations are necessary to assess children with neonatal hyperthyroidism and hypothyroidism's long-term cognitive, emotional, and behavioral development.

Due to the small group population, additional long-term research on large patient cohorts are required to better understand the natural history of AIT and to discover predictive variables for therapeutic intervention.

Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of University of Medicine and Pharmacy of Craiova (approval no. 6/20.01.2021).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Written informed consent has been obtained from the patient(s) to publish this paper.

Data Availability Statement

The data presented in this study are available on request from the corresponding authors.

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Conflict of Interest

None to declare.

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