

Impact of COVID-19 Pandemic on Congenital Hypothyroidism, Review of Neonatal Screening in Some States

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Abstract

Objective: The purpose of this work was to present some cases diagnosed with congenital hypothyroidism during a certain period of critical condition of covid 19 pandemic brought to our Department.

Methods: Data were extracted from retrospective analysis of patients diagnosed with congenital hypothyroidism brought to the Department of Nuclear Medicine for thyroid scan in order to detect the location of the thyroid tissue of the newly discovered newborn with congenital hypothyroidism.

Results: During the period April 17 to August 29, 2020, 5 newborns were diagnosed with congenital hypothyroidism. Clinical evaluation of patients was performed, performing additional routine examinations at all times according to the clinical and diagnostic route. All cases came with results from thyroid hormone testing samples with TSH > 100. In our ward the patient undergoes ultrasonography and thyroid scan. The mean age of diagnosis was 25.5 days. Ectopic sublingual glands were found in three patients with ultrasonography and thyroid scan was confirmed in three patients. One patient with ultrasonography alone was suspected of hypoplasia of the thyroid gland, while with thyroid scan in two patients, one after starting replacement therapy and scintigraphy was done without this information and we gained weak fixation of radionuclide at the level of the newborn neck, where is suspected in the absence of thyroid gland tissue, and in the other case we had poor fixation consistent with ultrasound. We in one patient had thyroid gland deficiency.

In February 2022, in one case on ultrasonography we had the clear image of the appearance of two lobes with heterogeneous microgranular ecostructure, with hypervascularization and on thyroid scan we had intense fixation in both lobes.

Conclusions: Ultrasonography and scintigraphy of the thyroid gland play an important role in diagnosing the ectopic tissue identification or absence of the thyroid gland, and the impact of the critical condition of covid 19 pandemic remains a challenge to be analyzed. All patients diagnosed in the Department of Nuclear Medicine have continued visits and treatment by pediatric endocrinologists.

Keywords: COVID-19; Congenital Hypothyroidism; Scintigraphy and Ultrasonography of the Thyroid Gland; Neonatal Screening Review in Some States

Introduction

Significant physiological changes in thyroid hormones (THs) of pregnant women occur during pregnancy (Fan., *et al.* 2019) [1]. Around the fifth or sixth week of pregnancy, although the fetal thyroid has begun to develop, the fetus is not yet able to synthesize its own THs at this time (Patel., *et al.* 2011) [2]. In the first and early part of the second trimester, fetuses rely entirely on the mother's supply of TH (Chen., *et al.* 2015) [4]. Whereas from the middle of the second trimester onwards, the original maternal and fetal THs are present in the fetus (Chan., *et al.* 2009) [3]. Therefore, fetal TH needed for normal neurological development comes exclusively from the mother.

T3 and T4 exert effects not only on fetal development but also on placental function (Landers., *et al.* 2009; Li., *et al.* 2010; Chen., *et al.* 2015) [4,5,16].

There has been a trial of the use of T3 for the treatment of patients with critical illness with COVID-19 infection (Pantos., *et al.* 2020) [6].

Inflammation caused by SARS-CoV-2 can become a risk factor for pregnancy, leading to T3 deficiency in the placenta and fetus. Moreover, the main regulator of TH homeostasis in the placenta is D3 (Adu-Gyamfi., *et al.* 2020) [7], which protects the fetus from an overexposure to T3.

Current studies suggest that SARS-CoV-2 infection alters thyroid function in early pregnancy and that there is an increased risk of adverse pregnancy outcomes (Lin., *et al.* 2020) [8]. The relationship between ACE2 expression levels during SARS-CoV-2 infection is complex, with high ACE2 expression favoring the entry of SARS-CoV-2 host cells, whereas reduced ACE2 expression after infection can lead to severe disease (Ni., *et al.* 2020) [9]. THs play a key role

in determining the expression of ACE and ACE2 in plasma and various tissues, which in turn may play a role in the severity of SARS-CoV-2 infection and disease (Kumari., *et al.* 2020) [10]. Therefore, TH levels in COVID-19 pregnant women are of interest.

D3 activity may vary in the context of inflammation. During acute and chronic inflammation and during sepsis, liver Dio3 mRNA expression and activity levels are decreased (de Vries., *et al.* 2015) [11]. If there is a similar case within the placenta during inflammation caused by SARS-CoV-2, it may adversely affect the fetus due to overexposure to T3. In particular, there is an observation that suggests a possible attenuation of D3 activity in preeclampsia (Kurlak., *et al.* 2013) [12].

Abnormal regulation of the placental D3 gene is a potential contributor to fetal hypothyroidism because the more active D3 remains, the less active TH will be transferred to the fetus (Wilcoxon and Redei, 2004) [13]. High regulation of D3 is rarely seen and usually occurs in conditions of critical illness or prolonged inflammation (de Vries., *et al.* 2015) [11], but further study showed that prolonged reduction of food intake during illness may be the predominant cause for adjustment of D3. de Vries., *et al.* 2014) [14]. Therefore, it can serve as a reminder that during infection and SARS-CoV-2 treatment, pregnant women should better avoid fasting for a long time.

For pregnant women, more TH is required to maintain the concentration of hemostasis during pregnancy due to the physiological change of thyroid economy (Glinoeer., *et al.* 2010) [15].

Timely sampling for thyroid hormone measurement and rapid analysis and communication of results are key points for organizing a neonatal congenital hypothyroidism (CH) screening program. Thus the possibility of measuring thyroid hormones from blood dried on filter paper paved the way for the identification of new-

borns with congenital hypothyroidism (CH) from the first days of life. Consequently, the early initiation of adequate replacement therapy paved the way for an effective prevention of mental retardation (Torresani T., et al. 2014) [17].

Timely diagnosis, adequate treatment and regular follow-up of thyroid hormone tests in patients with congenital hypothyroidism, in order to achieve optimal results, obviously requires a close and well-planned harmonization of pediatric care in adult medicine, certainly always based on updates of the consensus guidelines to be used to further optimize the detection, diagnosis, treatment and follow-up of children with all forms of congenital hypothyroidism (CH) in the light of the latest evidence.

The recommendations include the various neonatal screening approaches for CH as well as the etiology (also genetics), diagnostics, treatment, and prognosis of both primary and central CH. When CH is diagnosed, the expert panel recommends the immediate start of correctly dosed levothyroxine treatment and frequent follow-up including laboratory testing to keep thyroid hormone levels in their target ranges, timely assessment of the need to continue treatment, attention for neurodevelopment and neurosensory functions, and, if necessary, consulting other health professionals, and education of the child and family about CH. Harmonization of diagnostics, treatment, and follow-up will optimize patient outcomes. Lastly, all individuals with CH are entitled to a well-planned transition of care from pediatrics to adult medicine.

Based on the updating of practical guidelines for the diagnosis and management of congenital hypothyroidism (CH) taken from an ENDO-European Reference Network (ERN) initiative launched that was approved by the European Association for Pediatric Endocrinology and the European Association for Endocrinology with 22 participants from ENDO -ERN and both companies (van Trotsenburg P., et al. 2020) [18].

Methods

Based on the study, we received the results of thyroid hormone analysis FT3, FT4, TSH performed before imaging studies of the thyroid gland in the newborn. Ultrasonography and scintigraphy of the thyroid gland with ^{99m}Tc - with diagnostic dose of 0.2-0.3mCi according to the patient's body weight. Ecam Simens dual-head Gamma camera was used to perform the scintigraphy, Detector 1 with wide field and high resolution collimator was used, Matrix size 128x128, Zoom 1.23, with 200 Kcts or 5 min., in supine posi-

tion an set position and sitting in cases where the doctor had to hold the baby to get the best view.

Results

With ultrasonography in three cases we were able to identify the ultrasonographic image of the residual sublingual gland, which were also verified by thyroid scan in four patients. In one case we had suspicions with ultrasonography but in scintigraphy we did not gain any suspicious fixation of radionuclide in the neck region. This baby had received it the day before the 50 mcg L-thyroxine replacement therapy from the endocrinologist pediatrician, remains as a pretext for not receiving the scintigraphic image. In one case we had hypoplasia (functional mass greatly reduced in both images), in one case we obtained the clear ultrasonographic image in terms of diffuse microgranular goiter slightly heterogeneous and slightly "pseudolobular", with quite pronounced vascularization as radionuclide intensities in both lobes of the thyroid gland and in one case we did not see thyroid gland tissue either by ultrasonography or by thyroid gland scintigraphy.

Detection of congenital hypothyroidism in infants of mothers who were positive for covid-19 on the eve or onset of pregnancy, where four of the mothers received two doses of the Pfizer vaccine in the fifth and sixth months of pregnancy (one infant resulted in dysormonogenesis and hypothyroidism despite the fact that we had ultrasonographic and scintigraphic presentation of the thyroid gland but with imaging elements characteristic of the inflammatory process of thyroiditis if it can be said "transcongenital", with a TSH > 100, where the baby's mother also had inflammatory changes in the thyroid gland, with TSH > 7 and ATPO > 1000. In a baby with scintigraphy we did not have the presentation of functional thyroid gland tissue in its own place, also the mother of the baby in question had elements of postnatal thyroiditis (with transient hyperthyroidism - weight loss, Suppressed THS and thyroid hormones slightly above the level of normal values, but clinically had started to show signs at discrete hypometabolic). In this case the baby was diagnosed as soon as he was two months old and the baby had visible initial signs of a change in appearance on the face. The mother of this baby had covid 19 in the first trimester of pregnancy. In three newborns we discovered the sublingual ectopic gland, where three mothers had covid 19 on the verge of pregnancy and received two doses of anti-covid vaccine 19 in the 5th and 6th month of pregnancy, and in one baby we had hypoplasia of the thyroid gland, whose mother had covid 19 in the 4th month of pregnancy.

No=7	Gender	Ambulance	From the hospital
Female	6	3	3
Male	1	0	1

Table 1: Classification by gender and according to instructions received in our.

Graph 1: Classification by gender and according to instructions received in our

No=7	Covid 19 +	Two doses of Faizer vaccine in the 5 th - 6 th month of pregnancy	Two doses of Faizer vaccine in the 7-8 th month of pregnancy	Without vaccination
On the eve of pregnancy	2	2	0	0
In early pregnancy	1	1	0	0
In the first trimester of pregnancy	3	1	2	0
In the fourth month of pregnancy	1	0		1
N0. Total	7	4	2	1

Table 2: Mothers infected with covid 19 and vaccinated during pregnancy.

Graph 2: Mothers infected with covid 19 and vaccinated during pregnancy.

Graph 3: Ultrasonographic and scintigraphic findings.

N0=7 patients Hypothyreosis Congenitalis	Discovery	Ultrasonography	Thyroid scan (99mTc)
Sublingual	3	3	3
Suspicious in the rudimentary tissue of the thyroid gland/hypoplasia	2	1	(2-without fixation) poor fixation (L-thyroxine 50 mcg)
Diff, Thyroiditis (Hyperplasia)	1	1	1
Lack of thyroid gland (agenesis)	1	1	1

Table 3: Ultrasonographic and scintigraphic findings.




Image 1: Ectopic sublingual goiter.

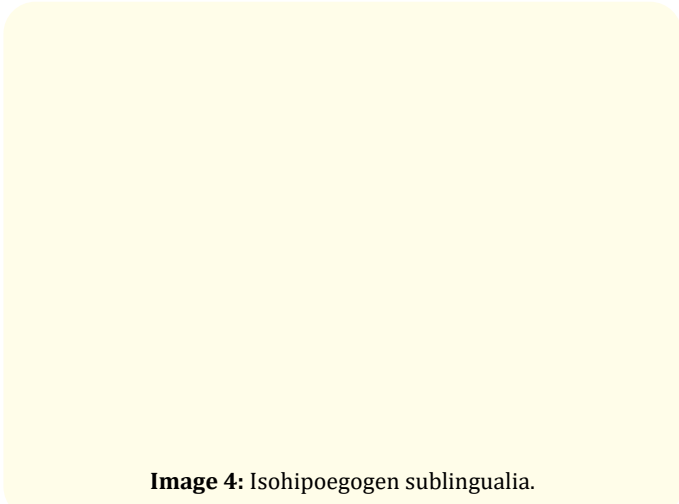


Image 4: Isohipoegogen sublingualia.

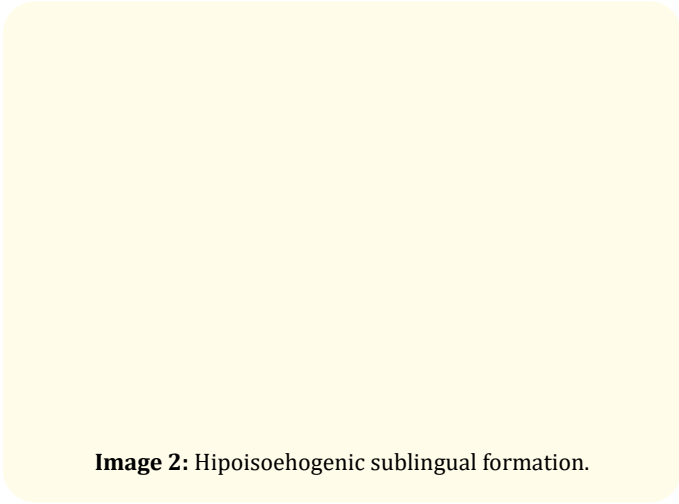


Image 2: Hipoisoehogenic sublingual formation.

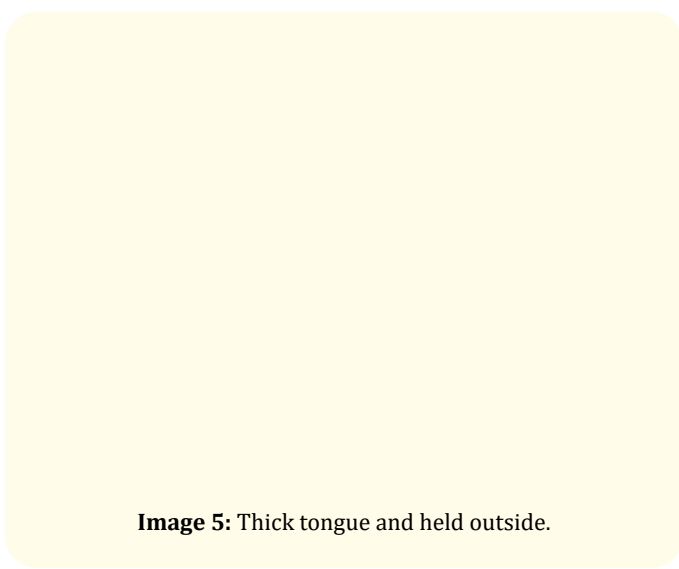


Image 5: Thick tongue and held outside.

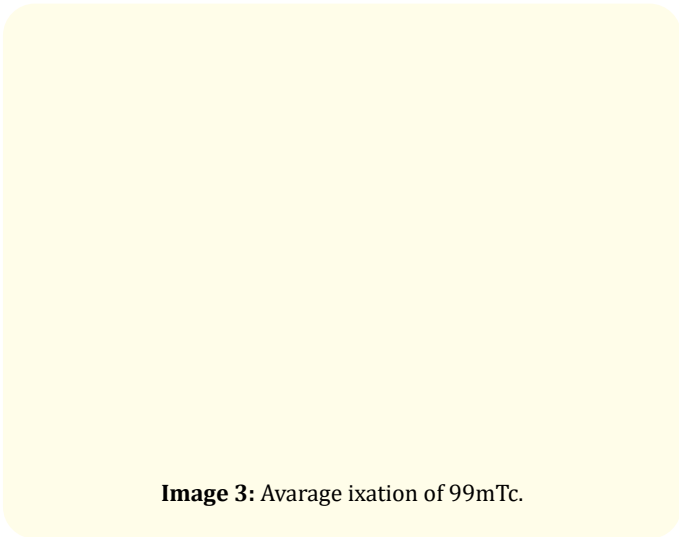


Image 3: Average fixation of 99mTc.

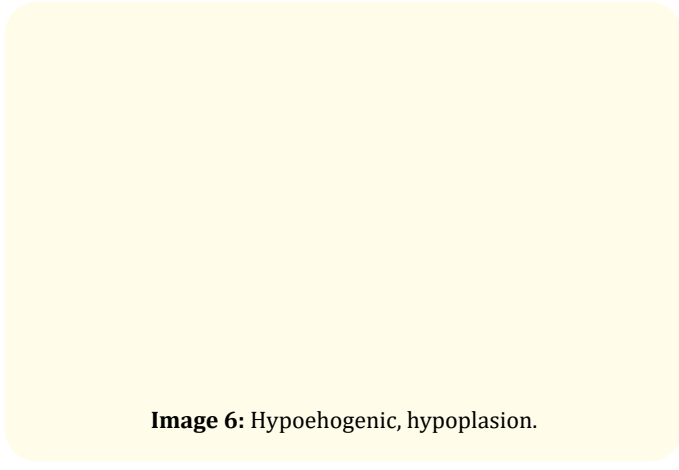


Image 6: Hypoehogenic, hypoplasion.

Image 7: The patient who was given 50 mcg L-thyroxine one days before thyroid scan.

Image 8

Image 9: Heterogeneous micro granular diffuse hypertrophy.

Image 10: Increased vascularization.

Image 11: Diffuse goiter with ^{99m}Tc hyperfixation.

Discussion

This work can be said for 6 cases was relatively timely detection with congenital hypoparathyroidism and one case after filling two months of infants of mothers who were positive with covid-19 in near or early pregnancy and who received vaccines anti covid 19 during pregnancy. We hope to influence the health authorities in further epidemiological and experimental studies which are needed to understand the increasing incidence of this condition and to investigate more about the impact of affected mothers on the eve of pregnancy or in its onset with covid-19, as well as the impact of vaccination in certain months of pregnancy. Perhaps this study of ours may be a coincidence, but comparing with the cases of detection and diagnosis of babies with congenital hypothyroidism in the early years in our country which numbers approximately 180,000 to 200,000 inhabitants, where the number of which was much lower within a year compared to 2021 for a very short period of time April-August (4-5 months) were 6 babies and one case detected in early February 2022, or within 10 months to count 7 cases of congenital hypothyroidism. Since we lack basic data or connection to the general information of neonatologists and pediatric endocrinologists, endocrinologists or even gynecologists and imaging physicians, we can not say exactly about the incidence and impact of possible factors.

Of the 7 newborns referred to our Service, diagnosed with increased neonatal thyroid stimulating hormone (TSH), ultrasound findings and thyroid scan with etiology have resulted: agenesis in one (0.14%); ectopy in three (0.42%); hypoplasia in 2 (0.28%); and hyperplasia in 1 (0.14%).

Compared to the incidence of the state of Turkey and Italy, where the percentages are higher, of course these values can not be approximate because we do not have the exact number of ba-

bies born, and for this period of time during the pandemic crisis with covid 19, most babies are also born in private sector hospitals. Also, since we do not have a screening test (it is not applied yet), and it remains that the mother herself or any random check-ups by the neonatologist or pediatrician have discovered the signs. In these circumstances we can not give the values of newborns with transient hypothyroidism or estimate the degree of diagnosis in the first month, as described in studies of these two states which turned out to be 87%. The etiological incidence of dysgenesis and dishormonogenesis was equal to 33.3%. and had the majority of cases with normal thyroid gland which are diagnosed with transient hypothyroidism.

However we make a comparison with the Etiology in patients diagnosed only with neonatal TSH raised in admission to us: agenesis we had a lower% compared to the Turkish state (about 0.14%), while in Turkey by the total number of tested have had one (2.08%); ectopies we lead with a very high percentage of about 0.42% in relation to (2.08%); hypoplasia in us we detected in 0.28% while the Turkish state had a higher percentage around (29.16%); and hyperplasia we had 0.14% whereas those with a high percentage around (33.3%).

- But the average age of detection and the beginning of treatment of infants
- Diagnosed as a result of the initial assessment is not strongly different from the Turkish state where it was 22.13 days, while in our cases 25.5 days(19. Cases Referred from the Turkish National Screening Program: Frequency of Congenital Hypothyroidism and Etiological Distribution [19].

Conclusion

Certainly the use of consensus guidelines to further optimize the detection, diagnosis, treatment and follow-up of pregnant women first by gynecologists and endocrinologists to adequately diagnose and treat mothers during pregnancy and of course children with all forms of congenital hypothyroidism (CH) always considering the importance of using the newborn screening test, (in our country it is absent), and referring to all neonatologists and pediatricians endocrinologists, endocrinologists and physicians in certain imaging fields, to use the latest evidence of guidelines in order to avoid consequences.

We hope to influence the health authorities in further epidemiological studies

Close collaboration between researchers in further research, laboratory specialists, pediatric endocrinologists and genuine imaging diagnostics to determine if monitoring and treatment will provide a treatment that will lead to safe and effective results. It obviously requires a complex interaction and cooperation, starting from the family doctor to the endocrinologist.

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