Evaluation of Thyroid Function Tests in Children With Covid-19

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Research Article

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Abstract

Objective: The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2, has rapidly spread around the world since December 2019. Coronaviruses are known to have direct effects on various endocrine glands, including the thyroid gland. Although adult studies provide useful information and most of these studies are compatible with Non thyroidal illness, there were no data analysed throid function tests in children with COVID-19.

Aim: We aimed to evaluate the levels of free T4 (fT4), free T3 (fT3), thyrotropin (TSH) and thyroid autoantibodies during and after the disease in children with COVID-19.

Methods: We studied 18 patients followed up in our pediatric infectious diseases clinic and pediatric endocrinology clinic with the diagnosis of COVID-19 between September-December 2021. In these patients with COVID-19 a standard set of blood tests including complete blood count, kidney, liver function, thyroid function and thyroid auto antibodies were performed. After 3 months later, we tested thyroid function, thyroid auto antibodies again.

Results: In thyroid function tests taken during the disease, fT4 of all patients was normal. fT3 was low in 6 (33.3%) patients, and TSH was high in 2 (11.1%) patients. In the control tests performed 3 months later, TSH of all patients was normal. Control fT4 was low in 2 (11.1%) patients whose fT4 was normal during the disease. In 5 (27.7%) patients control fT3 was found low. When the relationship of these parameters with the infection criteria was examined, a negative correlation was found between fT3 taken at the time of COVID-19 positive and CRP, and a positive correlation between fT3 and absolute lymphocyte counts at the 3rd month control.

Conclusion: Abnormalities in the examinations taken during the disease were mostly found to be compatible with sick euthyroid syndrome. The persistency of low fT3 and newly detected fT3 and fT4 decreases in the follow up suggested involvement of hypothalamo pituitary-thyroid axis due to Covid 19.

What Is Known?

What is Known?

COVID-19 has serious effects on multiple organs and systems have been known. Coronaviruses directly may effect various endocrine glands, including the thyroid gland. Most of adult studies investigating thyroid gland involvement by COVID-19 are compatible with non thyroidal illness.

What is New?

In this study, thyroid function tests were evaluate in children with COVID-19. We performed thyroid function tests again 3 months later to differentiate results from non thyroidal illness. Also, we testted thyroid auto-antibodies in children with COVID-19 to evaluate autoimmune involvement.

Introduction:

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly spread around the world since December 2019. World Health Organization announced the COVID-19 outbreak as a pandemic on 11 March 2020. A number of serious effects on multiple organs and systems have been reported [1]. Coronaviruses are known to have direct effects on various endocrine glands, including the thyroid gland. In patients infected with severe acute respiratory syndrome coronavirus (SARS-CoV), damage to the follicular and parafollicular cells of the thyroid was demonstrated at post-mortem [2]. Additionally, coronaviruses have been detected in the pituitary gland post mortem [3], and decreased staining for thyrotropin (TSH) has been observed in the anterior pituitary gland of patients with SARS-CoV [4]. SARS-CoV-2 enters cells via the angiotensin converting enzyme 2 (ACE2) receptor. ACE2 receptor is highly expressed in the thyroid gland. Therefore, the hypothalamic-pituitary-thyroid axis may be prone to disruption in COVID-19 patients [5].

Although adult studies provide useful information and most of these studies are compatible with non thyroidal illness (NTI) [6, 7], there were no data analysed throid function tests in children with COVID-19. They had incomplete data, for example, did not measuring thyroid autoantibodies. In line with this information, in this study, we aimed to evaluate the levels of free thyroxine (fT4), free triiodothyronine (fT3), TSH and thyroid autoantibodies during and after the disease in children with COVID-19.

Materials And Methods:

This prospective study was approved by the Clinical Research Ethics Committee of Izmir Tepecik Training and Research Hospital, Health Sciences University (reference number:). The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Eighteen children with Covid – 19, age was 1 month to 18 years admitted to our clinic in September-December 2021 were included in this study. In these patients with COVID-19 were performed a standard set of blood tests including complete blood count, kidney function, aspartate aminotransferase (AST), alanine aminotransferase (ALT), c-reactive protein (CRP), ferritin, d-dimer, lactic dehydrogenase (LDH), fT4, fT3, TSH and thyroid auto-antibodies. Demographics and clinical datas of interest (age, sex, puberty, weight, height) were recorded. COVID-19 diagnosis was defined as a real-time reverse transcriptase polymerase chain reaction confirmation of infection from a nasopharyngeal swab. 3 months later, fT4, fT3 and thyroid auto-antibodies testes were performed again during outpatient controls.

Assay methodology:

Fasting venous blood samples were obtained from all subjects to evaluate biochemical parameters including plasma glucose, urea, creatinine, AST, ALT, CRP, LDH and ferritin, as well as hormones including fT3, fT4, TSH, anti-thyroglobulin (anti-TG) and anti-thyroperoxidase (anti-TPO) antibodies. Glucose, urea, creatinine, AST, ALT, CRP, LDH and ferritin levels were measured by enzymatic methods using an AU5800 autoanalyzer (Beckman Coulter Inc., CA, USA). fT3, fT4, TSH levels, were analysed by chemiluminescence

assay method using a DxI immunoanalyser (Beckman Coulter Inc., CA, USA). Thyroid-stimulating hormone level was 0.34–5.76 mIU/L in all age ranges. Free triiodothyronine level was 3.6–7.5 ng/dL in the first year, 4.3–6.8 between one and 12 years, 3.8–6.7 between 12 and 15 years, and 3.5–5.9 ng/dL between 15 and 18 years. The free thyroxine level was 0.5–2.3 between one month and two years and 0.7–1.6 ng/dL between two and 18 years. Anti-TPO antibody level was 0–10 IU/mL and anti-TG antibody level was 0–5 IU/mL in all age groups.

Statistical analysis:

Measurement values were given as mean ± SD and median. The compatibility of the data with the normal distribution evaluated with the Kolmogrov-Smirnov test, and the coefficients of steepness and skewness were evaluated. In cases where parametric conditions were met, repeated measurements, in-group and between-group comparisons of paired groups, and paired independent samples t-test were used. In cases where parametric conditions were not met, Mann Whitney-U and Wilcoxon tests were used, and if necessary, the relationship was determined with the Pearson correlation test. Chi-square test was applied on the variables indicated by count. The analyzes of the existing data was carried out using the IBM SPSS 24 program (Statistical Package for Social Sciences, Chicago, IL, USA) according to the group characteristics, and the significance level was accepted as $p < 0.05$ in all statistical tests. In addition, the differences between the measurements according to time were evaluated by analysis of variance in repeated measurements. G*power 3.1 program was used to determine the number of samples to be included in the study.

Results:

In our study, 12 (67%) patients were female. Mean age of the patients was 11 ± 0,7 and 12 (67%) of the patients were pubertal (Table 1). In thyroid function tests taken during the disease, fT4 of all patients was found normal. fT3 was low in 6 (33.3%) patients, and TSH was high in 2 (11.1%) patients. In the control tests performed 3 months later, TSH of all patients was the normal. It was observed that the TSH elevation detected in 2 patients returned to normal. Control fT4 was found to be low in 2 (11.1%) patients whose free T4 was normal during the disease. In 5 (27.7%) of patients, control fT3 was found low. When the relationship of these parameters with the infection criteria was examined, a negative correlation was found between fT3 taken at the time of COVID-19 positive and CRP, and a positive correlation between fT3 and absolute lymphocyte counts at the 3rd month control (Table 2).

Table 1
Demographic features of Patients with COVID-19

	(n = 18)
Gender (male)*	6 (33)
Age (months)**	11 ± 0,7
Pubertal*	12 (67)
Height (cm)**	141,5 ± 39,3
Height SDS**	0,35 ± 0,59
Weight (kg)**	46,6 ± 28,4
Weight SDS**	0,25 ± 1,64
BMI SDS**	0,14 ± 1,82
SDS: standart deviation score, SD: standart deviation.	
*n, % **mean ± SD	

Table 2
Comparison of TFT Results of Patients with COVID-19 Infection and After Three Months Follow-up

	COVID-19 + **(n = 18)**	**Follow-up** **(n = 18)**	***P* Value**
fT3 (pg/ml)*	3,83 ± 0,55	3,99 ± 0,56	0,393
fT4 (ng/dl)*	0,90 ± 0,12	0,84 ± 0,14	0,182
TSH (mIU/L)*	2,95 ± 2,20	2,87 ± 1,06	0,861
Anti-TG (IU/mL)*	0,54 ± 0,47	0,59 ± 0,37	0,617
Anti-TPO (IU/mL)*	0,70 ± 0,34	0,9 ± 0,00	0,177
TFT: Thyroid Function Tests, TSH: Thyroid stimulating hormone, fT3: Free triiodothyronine, fT4: Free thyroxine, Anti-TPO:Anti-Thyroid Peroxidase, Anti TG: Anti-Thyroglobulin SD: standart deviation.			
*mean ± SD			

Table 3
Correlation of Infection Parameters with TFT

		ALS	ANS	CRP	FERRITIN	CK	LDH	D-DIMER	FB
fT4	r	0,225	-0,117	-0,042	0,346	0,238	0,308	0,191	0,094
COVID +	p	0,370	0,643	0,870	0,189	0,342	0,214	0,448	0,710
fT3	r	0,298	-0,398	**-0,692***	0,213	0,194	-0,224	-0,300	0,194
COVID +	p	0,230	0,102	**0,001**	0,428	0,440	0,372	0,226	0,440
TSH	r	0,160	-0,277	-0,284	0,182	0,403	-0,187	-0,232	0,137
COVID +	p	0,526	0,265	0,254	0,499	0,097	0,458	0,355	0,586
sT4	r	0,062	0,080	-0,041	0,142	-0,034	– 0,315	-0,423	0,279
Follow-up	p	0,807	0,754	0,754	0,600	0,893	0,202	0,080	0,263
sT3	r	**0,577***	0,155	-0,313	0510	0,132	0,104	-0,260	0,323
Follow-up	p	**0,024**	0,580	0,256	0,075	0,639	0,712	0,349	0,241
TSH	r	-0,097	-0,274	-0,321	0,149	0,185	-0,247	-0,206	0,088
Follow-up	p	0,702	0,271	0,195	0,581	0,462	0,323	0,412	0,728

ALC: Absolute lymphocyte count, ANS: Absolute neutrophil count, CRP: C-reactive protein, CK: Creatınıne kınase, LDH: Lactate dehydrogenase, FB: Fibrinogen, TFT: Thyroid Function Tests, TSH: Thyroid stimulating hormone, fT3: Free triiodothyronine, fT4: Free thyroxine,

Discussion:

Recently, there have been reports of the potential relationship between COVID-19 and thyroid dysfunction in adults. In a Chinese study, Chen et al.[6] reported the levels of TSH and serum total triiodothyronine (TT3) of the patients with COVID-19 were significantly lower than those of the healthy control group and non-COVID-19 pneumonia patients and the more severe the COVID-19 had the lower the TSH and TT3 levels. In another study, Khoo et al. [7] observed mild reductions in TSH and FT4 in keeping with NTI but most of patients with COVID-19 were euthyroid. Furthermore, in survivors of COVID 19, thyroid function tests at follow-up returned to baseline. In our study, fT3 was found low consistent with NTI in 6 patients in the first tests during the disease. However, in controls tests, taken after 3 months when subjects were healthy; in 3 patients, low fT3 continued and in 2 patients, newly detected low fT3 was detected. On the other hand, fT4 was found low in two patients whose initial tests during the disease were normal. There were a negative correlation was found between fT3 taken at the time of COVID-19 positive and CRP, and a positive correlation between 3rd month control fT3 and absolute lymphocyte counts. Although all of our patients were mild, this relationship between infection criteria and fT3 suggested that there may be a relationship between disease severity and impairment in thyroid function tests, as in adult studies in the literature.

The dysregulated immune response and increased pro-inflammatory cytokines excited by SARS-CoV-2 conduce to the disease pathogenesis and organ damage [8]. The medications to treat autoimmune diseases such as steroids are common used in critical cases of COVID-19 [9]. Besides, several autoantibodies can be detected in patients with COVID-19 [10]. These findings suggest that COVID-19 can be trigged autoimmune diseases. Hashimoto's thyroiditis, is a most cammon autoimmün diseases and it's pathogenesis has not been fully lightened. Further studies suggest that a potential trigger may be dysfunction of CD4 + CD25 + differentiating regulatory T cells (Tregs) [11]. Tregs are determined by the expression of the transcription factor Forkhead Box P3 (FOXP3), suggesting that it is in the context of abnormal expression of FOXP3 that the autoimmune process in question may be caused. FOXP3 is negatively regulated by SIRT1, a nicotinamide adenine dinucleotide-dependent protein deacetylase [12, 13]. In an inflammatory process, there is a serum increase in circulating proinflammatory interleukins, which supports an increased oxidative stress scenario, leading to damaged signalling in the SIRT1 pathway [14]. Based on this data in the literature, we suggested that there might be a relationship between Covid 19 and Hashimoto's disease. Therefore we performed thyroid autoantibodies from the patients both at the time of disease and 3 month later but we did not detect elevation in thyroid antibodies in any of the patients.

To our knowledge, in this study, thyroid function tests were evaluate of first time in children with COVID-19. We also performed thyroid function tests 3 months later to differentiate results from NTI and evaluate their longer effects on thyroid function tests. In addition, we testted thyroid auto-antibodies in children with COVID-19 to evaluate autoimmune involvement for the first time.

Limitations of this study are the limited number of patients and the lack of thyroid ultrasonography. But we were working on a contagious disease as a result we had to minimize the number of patients and procedures.

In conclusion, abnormalities in the examinations taken during the disease were mostly found to be compatible with sick euthyroid syndrome. The persistency of low fT3 and newly detected fT3 and fT4 decreases in the follow up suggested involvement of hypothalamo pituitary-thyroid axis due to Covid 19.

Abbreviations:

ACE2: Angiotensin converting enzyme 2

ALT: Alanine aminotransferase

anti-TG: Anti-thyroglobulin

anti-TPO: Anti-thyroperoxidase

AST: Aspartate aminotransferase

CRP: C-reactive protein

COVID-19: The coronavirus disease 2019

FOXP3: Forkhead Box P3

fT3: Free triiodothyronine

fT4: Free thyroxine

LDH : Lactic dehydrogenase

NTI : Non thyroidal illness

SARS-CoV: Severe acute respiratory syndrome coronavirus

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

TSH : Thyrotropin

TT3: Total triiodothyronine

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Authors' contributions: AS: Drs Dündar, Ayrancı, conceptualized and designed the study, collected data drafted the initial manuscript, reviewed, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

Drs Çatlı, Manyas, Tüz, Çolak, Yılmaz, Yıldırım-Duman designed the data collection instruments, collected data, critically reviewed the manuscript for important intellectual content, and revised the manuscript.

Ethics approval: This study was approved by the Health Sciences University Tepecik Training and Research Hospital Ethical Committee (Decision number: 2021/03-28).

Consent to participate: Consent was obtained from the patients and parents.

Consent for publication: Consent was obtained.

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