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Thyroid Function Test Abnormalities in Children and Adolescents with COVID-19: A Case-Control Study

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Abstract

Background: There is a lack of conclusive evidence regarding thyroid function test (TFT) abnormalities in COVID-19, especially among children.

Objectives: This study aimed to investigate TFT abnormalities in COVID-19 pediatric patients compared to healthy children.

Methods: This study was conducted on 37 COVID-19-positive children who were admitted to Namazi Hospital from January 21 to March 1, 2022, compared with 37 healthy children. Within 48 h of positive real-time polymerase chain reaction (PCR) results for severe acute respiratory syndrome coronavirus 2, a blood sample was taken to measure serum levels of thyroid-stimulating hormone (TSH) and total thyroxine (tT4) in the two groups. Additional tests, including free and total triiodothyronine, free T4, and thyroperoxidase antibodies, were also conducted on cases. The chi-square, Pearson correlation coefficient, and analysis of variance tests were used for data analysis.

Results: Twenty-five patients were male, and 49 were female, with a mean age of 7.99 ± 5.02. The abnormal TFT and TSH frequency was significantly higher in the case group than in the control group. Nevertheless, there was no significant difference between the case and control groups regarding tT4 abnormalities. We could not establish an association between the mean of TSH and tT4 and age groups in the two groups and between abnormalities of TFTs and COVID-19 severity.

Conclusions: Although abnormalities of TFT were significantly more common among COVID-19 children, they were not associated with the disease severity. However, studies with larger sample sizes are recommended to evaluate thyroid abnormalities and their clinical course in COVID-19 children.

Keywords: COVID-19, Thyroid Gland, Pediatrics, Thyroxine, Case-Control Studies

1. Background

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to affect the global community (1). Although it was initially believed that children are not seriously affected by COVID-19 (2, 3), as of June 1, 2022, the Centers for Disease Control and Prevention (CDC) has reported more than 13 million cases of COVID-19 and 1,533 COVID-19-associated deaths in children under 18 years old (4). Moreover, children are shown to experience similar clinical courses as adults (5). Approximately 75% of 0 - 17-year-old children and adolescents in the United States tested positive for SARS-CoV-2 by February 2022 (6), a prevalence higher than that of the adult population (33% to 64%) (7).

Although the disease is primarily known as a respiratory system infection (8, 9), several other organs, including the thyroid gland, can be infected by the virus. The thyroid gland expresses angiotensin-converting enzyme 2 (ACE2) receptor and transmembrane protease serine 2 (TMPRESS2), which are both involved in SARS-CoV-2 entrance and infection pathways (10). Furthermore, pathological studies on autopsy specimens have discovered the SARS-CoV-2 genome in thyroid gland follicular cells (11). These findings raised the hypothesis that the hypothalamic-pituitary-thyroid axis may be susceptible to disturbances in patients with COVID-19,

either by hypophysitis, the virus spread to the thyroid gland, excessive cytokine production, or just as a process associated with severe illness state and not specific to COVID-19 (10, 12). On the other hand, SARS-CoV-2 infection may induce autoimmunity by different mechanisms. Autoantibodies produced against the virus may exhibit cross-reactivity with host cells and trigger a type II hypersensitivity reaction (13). Moreover, the activation of T lymphocyte cells may lead to a type IV hypersensitivity reaction and cause tissue damage (14).

Autoimmune thyroid disorders are one the most important endocrine abnormalities of the autoimmune pathologies following COVID-19 infection. For example, subacute thyroiditis was reported following COVID-19 in some patients (15). Lui et al. also observed a few incidences of thyroiditis during the convalescence period of COVID-19 (16). Moreover, cases of concurrent Grave's disease and COVID-19 may also support the autoimmunity mechanism of thyroid involvement during SARS-CoV-2 infection (17, 18).

Thyroid function tests (TFTs) have been investigated by several studies in adult patients with COVID-19. A cross-sectional study reported abnormal TFTs among adults with COVID-19 as high as 67.7%, with sick euthyroid being the leading diagnosis (19). However, Lania et al. reported 25.4% abnormal TFTs in COVID-19 adults, who mainly had TFTs suggestive of thyrotoxicosis (20). Additionally, in a study by Chen et al., 56% of patients with COVID-19 demonstrated lower-than-the-normal-range thyroid-stimulating hypophysitis hormones (TSH). They showed that TSH and tT3 serum levels were also associated with disease severity (21).

Despite these studies, currently, there is a lack of conclusive evidence regarding TFT abnormalities in COVID-19, especially among children. To the author's knowledge, only one small study has investigated TFT abnormalities among 18 children with COVID-19 under 18 years. They reported 33.3% low fT3 and 11.1% high TSH on admission without any significant difference after three months of follow-up (22).

2. Objectives

Due to the importance of thyroid function abnormalities in children with COVID-19, this study aimed to investigate TFT abnormalities in pediatric patients infected with COVID-19 compared to healthy children. The relationship between COVID-19 severity and TFT abnormalities was also assessed.

3. Methods

3.1. Selection and Description of Participation

This cross-sectional study was conducted on 37 COVID-19-positive children admitted to the pediatrics emergency ward of Namazi Hospital of Shiraz University of Medical Sciences from January 21 to March 1, 2022, during the sixth COVID-19 epidemic wave in Iran. For the control group, 37 healthy patients without any underlying disease referred for their routine follow-up to Imam Reza Clinic of Shiraz University of Medical Sciences were randomly selected.

The inclusion criteria for cases were positive RT-PCR for SARS-CoV-2 and age between one month and 18 years. Control group participants were healthy individuals without any underlying disease, had negative RT-PCR for SARS-CoV-2, and were aged from 1 month to 18 years. All participants with a positive history of thyroid and other hormonal diseases that may affect thyroid function test results or patients on hormonal medication, less than one month or more than 18 years of age, concurrent illnesses that may affect thyroid hormones as a result of severe disease, and negative or unknown RT-PCR for SARS-CoV-2 were excluded.

3.2. Technical Information

Within 48 h of positive RT-PCR results for SARS-CoV-2, a seven-milliliter peripheral venous blood sample was taken from cases and sent to Shahid Motahri laboratory for serum levels of TSH, free and total Thyroxine (fT4 and tT4), free and total triiodothyronine (fT3 and tT3), and thyroperoxidase antibodies (TPOAb). Similar sampling for serum levels of TSH and tT4 was also performed for the control group. Reference intervals for the above parameters were used according to the children's age (23).

Children with COVID-19 were further classified into four subgroups. We classified COVID-19 patients based on a combination of clinical symptoms and The National Early Warning Score-2 (NEWS-2) scoring system (24), including upper respiratory tract infection (URI) signs and symptoms, level of consciousness (LOC), and vital signs (VS), including respiratory rate (RR), heart rate (HR), systolic blood pressure (SBP) (according to their age), temperature (T), and O_2 saturation (O_2sat). Therefore,

1. Mild cases were defined as patients with mild URI symptoms, normal LOC, and stable VS (age-defined RR, HR, SBP, T $\leq$ 37.7°C, and O_2sat $\geq$ 96%).
2. Moderate cases were defined as patients with URI symptoms, abnormal findings in respiratory system examination, normal LOC, and stable VS (age-defined RR, HR, SBP, with or without fever (T $>$ 37.7°C), and O_2sat 92 - 96%).

3. Severe cases were defined as patients with URI symptoms, changes in LOC, and unstable VS (age-defined RR, HR, SBP, T > 37.7°C, and O_2sat < 92%).

4. Critical cases were defined as children with acute respiratory distress or respiratory failure and those undergoing intubation or developing organ failure requiring intensive care unit (ICU) admission.

Finally, the TSH and tT4 serum levels were compared between COVID-19 and control groups. Furthermore, serum levels of TSH and thyroid hormones (fT4, tT4, fT3, and tT3) were tested for statistical significance between different age groups and COVID-19 severity groups. Based on TFT parameters (TSH, fT4, tT4, fT3, tT3, and TPOAb), the frequency of TFT patterns suggestive of thyrotoxicosis, hypothyroidism (either primary or secondary), sick euthyroid syndrome, or others (not matched with a single pattern) were tested for statistical significance between different age groups and COVID-19 severity groups.

3.3. Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS, version 18, Chicago, Illinois). The normal distribution of data was evaluated using the Kolmogorov-Smirnov test. Descriptive data were summarized using mean ± standard deviation (SD) for normally distributed data, median (interquartile range [IQR]) for abnormally distributed data, frequency, and percentage. Moreover, analytic data were analyzed by chi-square, Pearson correlation coefficient, and analysis of variance (ANOVA) tests. P-value < 0.05 was considered statistically significant.

4. Results

In this study, 74 participants in the case (n = 37) and control (n = 37) groups, with a mean age of 7.99 ± 5.02 years old, were included. Six (8.1%) participants were infants, 6 (8.1%) were toddlers, 16 (21.6%) were preschool, 29 (39.2%) were school-age, and 17 (23%) were adolescents. Twenty-five (33.8%) were male, and 49 (66%) were female. The two groups were matched in terms of gender (P = 0.461) and age (P = 0.459).

The frequency of abnormal TFT was significantly higher in the case group than in the control group (P < 0.001). Moreover, abnormal TSH was significantly more frequent among cases than among the controls (P = 0.041). However, there were no significant differences between the case and control groups regarding tT4 abnormalities (P = 0.556) (Table 1). There was no significant relationship between abnormal TFT and age groups in the case (P = 0.391) and control groups (P = 0.819).

There was no significant difference in the mean of TSH between the case (3.39 ± 2.76) and control groups (3.20 ± 2.13) (P = 0.749). Furthermore, there was no significant difference in the mean of tT4 between the case (8.14 ± 1.21) and control groups (8.78 ± 1.90) (P = 0.089).

In terms of COVID-19 severity, 11 (29.7%) cases were mild, 10 (27%) were moderate, 10 (27%) were severe, and 6 (16.2%) were critical. There was no difference in the mean of TSH, FT4, Ft3, T3, and T4 between different categories of COVID-19 severity (P > 0.05) (Table 2). This study found no significant relationship between abnormal TFT and COVID-19 severity (P = 0.435). There was no significant difference in the severity of COVID-19 between different age groups (P = 0.148).

Also, there was no relationship between the different categories of severity and T4, T3, FT3, FT4, and TSH results (Table 3). Table 4 shows patterns of abnormal TFT in COVID-19 patients.

5. Discussion

The present case-control study investigated the association between COVID-19 and TFT abnormalities among COVID-19 and healthy children. Our results showed that abnormal TSH and abnormal patterns of TFT, including abnormal TSH and tT4, were significantly more frequent among COVID-19 children than among healthy controls.

Although there is no similar controlled study in the pediatric population, consistent with our results, Chen et al. observed abnormal TFT and lower-than-normal TSH levels in adults with COVID-19 more frequently than in non-COVID-19 pneumonia patients and healthy individuals (21). Moreover, serum levels of TSH, tT3, and fT4 were lower among adults with COVID-19 than among non-COVID-19 pneumonia patients and healthy participants (21, 25). Nevertheless, in our study, the mean of TSH and tT4 serum levels were not significantly different between cases and controls. This finding may be because in pediatric patients, unlike adults, normal ranges of TSH and thyroid hormones, such as T4 and T3, are age-dependent.

Furthermore, although the mean age of our cases and controls were similar, age groups could not be exactly matched. Therefore, comparing mean serum levels of TSH or other thyroid hormones may be misleading, and it would be more reasonable to compare TFT parameters based on patients' age-defined reference ranges. However, our relatively small sample size and possible selection bias could also be responsible for this finding. Further controlled studies with larger sample sizes in pediatric

Table 1. Frequency of Abnormal TFT, TSH, and tT4 in the Case and Control Groups

Variables	Case	Control	P-Value [a]
Age (y), Mean ± SD	7.55 ± 5.89	8.42 ± 3.99	0.459 [b]
Gender, No. (%)			0.46 [c]
Male	11 (29.7)	26 (70.3)	
Female	14 (37.8)	23 (62.2)	
TFT, No. (%)			< 0.001 [c]
Abnormal	18 (21.6)	2 (5.4)	
Normal	29 (78.4)	35 (94.6)	
TSH, No. (%)			0.041 [c]
Abnormal	19 (51.4)	2 (5.4)	
Normal	18 (48.6)	35 (94.6)	
tT4, No. (%)			0.556 [c]
Abnormal	2 (5.4)	1 (2.7)	
Normal	35 (94.6)	36 (97.3)	
TSH, Mean ± SD	3.39 ± 2.76	3.20 ± 2.13	0.749 [b]
T4, Mean ± SD	8.14 ± 1.21	8.78 ± 1.90	0.089 [b]

Abbreviations: TFT, Thyroid function test; TSH, Thyroid stimulating hormones; T4, Thyroxine.
[a] P value was significant at < 0.05 level
[b] Independent *t*-test
[c] Chi-square test

Table 2. The Mean of TSH, FT4, Ft3, T3, and T4 in Different Categories of COVID-19 Severity

Variables	Severity				P-Value [b]
	Mild [a]	Moderate [a]	Severe [a]	Critical [a]	
TSH	2.55 (1.39 - 3.96)	2.76 (1.38 - 3.8)	2.91(1 - 6.94)	3.5 (1.33 - 4.57)	0.984
FT4	1.4 (1.1 - 1.7)	1.55 (1.27 - 1.8)	1.15 (1 - 1.62)	1.4 (1.25 - 1.65)	0.280
FT3	3.1 (2.3 - 3.6)	2.6 (2.15 - 3.3)	3.15 (2.52 - 4.02)	3 (2.37 - 3.55)	0.663
T3	140 (102 - 154)	100 (94.7 - 145)	100.5 (92.75 - 137.25)	110 (97.75 - 134.75)	0.413
T4	8.2 (6.5 - 8.9)	8.3 (7.65 - 9.10)	8.25 (7.4 - 8.92)	8.55 (7.92 - 9.52)	0.750

Abbreviations: TSH, thyroid stimulating hormones; T4, thyroxine.
[a] Median (Q1-Q3).
[b] P value from the Kruskal-Wallis test was significant at < 0.05 level.

settings are required to investigate how serum levels of TSH and thyroid hormones are altered in COVID-19.

A meta-analysis of COVID-19 adults stated a 2.46-fold increased probability of severe COVID-19 among those with thyroid abnormalities (26). However, this association is still controversial. For instance, two cross-sectional studies on COVID-19 adults found no significant difference in any of the parameters of the TFT between mild, moderate, and severe groups (19, 27). Conversely, Chen et al. showed that TSH and tT3 levels were lower in more severe forms of COVID-19 (21). Similarly, in a study by Khoo et al., TSH was lower among patients admitted to the Intensive Therapy Unit (ITU) than in those not admitted to the ITU (25). Furthermore, among 287 COVID-19 patients, the in-hospital mortality rate was significantly higher in those with normal TSH values than in patients with either thyrotoxicosis or hypothyroidism (20).

We could not establish a relationship between COVID-19 severity and abnormalities of TFT parameters or abnormal TFT patterns. Similarly, some studies on COVID-19 in adults also found no association (27) or varying levels of thyroid hormones among patients in the moderate to severe and critical groups (28). However, other studies have shown an association in this regard; adult patients with more severe COVID-19 had lower serum levels of TSH, tT3 (21), and fT3 (19). These inconsistent

Table 3. Relationship Between Different Categories of Severity and T4, T3, FT3, FT4, and TSH Results

Variables	Severity of COVID-19, No. (%)				P-Value [a]
	Mild	Moderate	Severe	Critical	
T4 group					0.240
Low	2 (18.2)	0 (0)	0 (0)	0 (0)	
Normal	9 (81.8)	10 (100)	10 (100)	6 (100)	
T3 group					0.294
Low	3 (27.3)	1 (10)	5 (50)	2 (33.3)	
Normal	8 (72.7)	9 (90)	5 (50)	4 (66.7)	
FT3 group					0.915
Low	1 (9.1)	1 (10)	2 (20)	0 (0)	
Normal	9 (81.8)	9 (90)	8 (80)	6 (100)	
High	1 (9.1)	0 (0)	0 (0)	0 (0)	
FT4 group					> 0.999
Low	1 (9.1)	0 (0)	0 (0)	0 (0)	
Normal	10 (90.9)	9 (90)	10 (100)	6 (100)	
High	0 (0)	1 (10)	0 (0)	0 (0)	
TSH group					0.431
Low	0 (0)	0 (0)	1 (10)	1 (16.7)	
Normal	10 (90.9)	9 (90)	6 (60)	4 (66.7)	
High	1 (9.1)	1 (10)	3 (30)	1 (16.7)	

[a] Fisher's exact test

Table 4. Abnormal TFT Patterns in the COVID-19 Group

TFT Pattern	No. (%)
Normal	18 (48.6)
Thyroiditis	6 (16.2)
Subclinical hypothyroidism	5 (13.5)
Overt hypothyroidism	1 (2.7)
Sick euthyroid syndrome	2 (5.4)
No specific pattern	5 (13.5)
Total	37 (100.0)

findings indicate that there may be possible confounding factors that are not recognized by the studies. For example, the use of different methods of severity classification may affect the results. Patients' duration of illness and medications might also impact TFT parameters.

Our study detected abnormal TFT in approximately half (51.4%) of COVID-19 children. Also, TFTs suggestive of thyrotoxicosis and hypothyroidism (overt and subclinical) were the two most common abnormalities (16.2%, each one), followed by sick euthyroid syndrome (5.4%). However, 13.5% of our COVID-19 patients had abnormalities in TFT parameters that did not match any typical pattern. It might be due to the coexistence of two or more thyroid disorders, resulting in a mixed pattern.

Similarly, among adult patients with concurrent COVID-19 and abnormal TFTs, thyrotoxicosis is also a common finding (20.2% and 9.1%) (20, 27). This condition may be due to thyroid gland inflammation during COVID-19. The inflammation might be triggered by the cytokine storm following SARS-CoV-2 infection, as Lania et al. have established a close relationship between thyrotoxicosis and higher serum interleukin-6 (IL-6) (20). Alternatively, based on pathological studies on autopsies of patients with COVID-19 (11), possible direct infection of SARS-CoV-2 on the thyroid gland could also be considered.

Concurrent thyrotoxicosis and COVID-19 are clinically highlighted by higher rates of thromboembolic events (29), atrial fibrillation, and possibly higher mortality rates and longer hospitalization (20). However, none of our patients showed symptoms relevant to thyrotoxicosis.

The sick euthyroid syndrome was also introduced as the most common finding among 164 COVID-19 adults with a mean age of 53.8 years (19). Reducing the body's catabolism, sick euthyroid syndrome, or non-thyroidal

illness (NTI) is an adaptive response to a systemic illness (30, 31). It is characterized by low fT3 values as a result of increased deiodination of T4 (32). With increasing the disease's severity, the TSH pulsatility is lost, and fT3 and fT4 will be depressed (33). However, when prolonged, this condition may worsen the patient's outcome (34).

Despite the exact unknown mechanism of NTI, the cytokine storm during the COVID-19 course may suppress TSH and lead to NTI. Elevations in pro-inflammatory cytokines such as IL-6 (19, 20), IL-2, TGF-β (35), and even physiological levels of cortisol (36) may be responsible for the incidence of NTI among COVID-19 patients. Furthermore, hypophysitis from infection of hypophysis with SARS-CoV-2 is another possible mechanism for the changes in serum TSH levels (12).

Although this is the first study that reported patterns of abnormal TFTs in children with COVID-19, common patterns of TFT in adult patients with COVID-19 are also a matter of conflict; most studies have reported normal TFT as the most common pattern in patients with COVID-19 (20, 25, 27). However, in a cohort of 456 participants, hypothyroidism (overt, subclinical, and secondary) was the most common abnormal TFT pattern among the COVID-19 group (8.1%) (25). Two other studies found that among COVID-19 adult patients with abnormal TFT, thyrotoxicosis was the most common finding (20.2% and 9.1%) (20, 27). On the other hand, in a cross-sectional study by Dabas et al., 67.7% of the patients had abnormal TFT patterns. The sick euthyroid syndrome was the most frequent presentation (53.7%), followed by hypothyroidism (8.53%) and thyrotoxicosis (5.5%) (19).

Regarding different patterns of thyroid gland involvement, it is noteworthy that children's immune systems may respond differently to SARS-CoV-2 infection. Some studies have shown that during COVID-19, children have lower T lymphocyte cell activation and a different "cytokine production profile" (37-39). Moreover, novel variants of SARS-CoV-2 may have different clinical and prognostic features (5). Therefore, future studies may focus on clinical manifestations and courses, immunological aspects, and outcomes of thyroidal involvement between adults and children.

Two main limitations of this study were the lack of follow-up and our relatively small sample size. Therefore, this study did not clarify the clinical course of thyroid abnormalities among children after the resolution of COVID-19. Secondly, in this study, healthy children were selected as the control group. This decision was made to minimize confounding factors that could arise from comparing the results with other infectious diseases and concurrent illnesses affecting the thyroid axis. Thirdly, our data are limited by the study's single-center design and the absence of fT4, fT3, tT3, and TPOAb for the control group and TSH receptor antibody (TRAb) for patients with thyrotoxicosis. Our center is a tertiary-level hospital, and a selection bias by including more moderate to severe COVID-19 patients may have occurred. It is possible that since the sampling was performed within the first 48 hours of a positive RT-PCR result, the classical and final effects of severe illness on thyroid hormones were not completely developed. Finally, during the COVID-19 pandemic, physicians had lower thresholds for intubation or ICU admission, which may have led to an overestimation of severe and critical cases.

5.1. Conclusions

The current case-control study showed that abnormalities of TFT and TSH were significantly more frequent among children with COVID-19 than in healthy controls. However, abnormalities of TFT or its parameters were not associated with the severity of COVID-19. The study is mainly limited by its small sample size. Future studies may investigate thyroid abnormalities and their clinical course during and after the resolution of COVID-19 in larger samples of pediatric patients.

Footnotes

Authors' Contribution: Zhila Afshar, Keivan Sahebi, and Hassan Foroozand contributed to the study concept and design and the preparation of the manuscript. Negar Yazdani contributed to the analysis and interpretation of data and the revision of the manuscript. Zhila Afshar, Keivan Sahebi, Hassan Foroozand, Seyedeh Sedigheh Hamzavi, Hossein Moravej, Homa Ilkhanipoor, and Anis Amirhakimi participated in data acquisition. All co-authors critically reviewed the paper and approved the submitted version.

Conflict of Interests: The authors declare that they have no conflict of interest.

Data Reproducibility: The dataset presented in the study is available on request from the corresponding author during submission or after publication. The data are not publicly available due to privacy.

Ethical Approval: The present study was approved by the Local Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1400.580).

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