ORIGINAL ARTICLE

DOI: 10.4274/jcrpe.galenos.2022.2022-4-7

J Clin Res Pediatr Endocrinol 2022;14(4):402-408

Are Thyroid Functions Affected in Multisystem Inflammatory Syndrome in Children?

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What is already known on this topic?

The health effects of the global Coronavirus disease-2019 (COVID-19) pandemic are still being investigated. In children infected with Severe acute respiratory syndrome-Coronavirus-2, the causative virus of COVID-19, a clinical condition has emerged, called multisystem inflammatory syndrome in children (MIS-C).

What this study adds?

This is the first study to investigate the relationship between MIS-C and thyroid function. Low free triiodothyronine levels were associated with both the diagnosis of MIS-C and severe clinical presentation.

Abstract

Objective: Multisystem inflammatory syndrome in children (MIS-C), associated with Coronavirus disease-2019, is defined as the presence of documented fever, inflammation, and at least two signs of multisystem involvement and lack of an alternative microbial diagnosis in children who have recent or current Severe acute respiratory syndrome-Coronavirus-2 infection or exposure. In this study, we evaluated thyroid function tests in pediatric cases with MIS-C in order to understand how the hypothalamus-pituitary-thyroid axis was affected and to examine the relationship between disease severity and thyroid function.

Methods: This case-control study was conducted between January 2021 and September 2021. The patient group consisted of 36 MIS-C cases, the control group included 72 healthy children. Demographic features, clinical findings, inflammatory markers, thyroid function tests, and thyroid antibody levels in cases of MIS-C were recorded. Thyroid function tests were recorded in the healthy control group.

Results: When MIS-C and healthy control groups were compared, free triiodothyronine (fT3) level was lower in MIS-C cases, while free thyroxine (fT4) level was found to be lower in the healthy group ($p < 0.001$, $p = 0.001$, respectively). Although the fT4 level was significantly lower in controls, no significant difference was found compared with the age-appropriate reference intervals ($p = 0.318$). When MIS-C cases were stratified by intensive care requirement, fT3 levels were also lower in those admitted to intensive care and also in those who received steroid treatment ($p = 0.043$, $p < 0.001$, respectively).

Conclusion: Since the endocrine system critically coordinates and regulates important metabolic and biochemical pathways, investigation of endocrine function in MIS-C may be beneficial. These results show an association between low fT3 levels and both diagnosis of MIS-C and requirement for intensive care. Further studies are needed to predict the prognosis and develop a long-term follow-up management plan.

Keywords: MIS-C, thyroid function, free triiodothyronine, free thyroxine

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Conflict of interest: None declared
Received: 15.04.2022
Accepted: 01.06.2022

Introduction

Multisystem inflammatory syndrome in children (MIS-C), associated with Coronavirus disease-2019 (COVID-19) in children, is defined as the presence of fever, inflammation, and organ dysfunction other than through microbial causes (1). The pathophysiological mechanisms for MIS-C are not yet clear. Severe inflammation, the time interval between Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) infection and MIS-C, high inflammatory markers, and response to various immunomodulatory treatments suggest an immunological reaction rather than a virus-mediated condition. In addition to the abnormal immune response against the virus, extensive vascular endothelial damage caused by viral infection also contributes to the pathogenesis of MIS-C (2). It remains unclear whether the multi-organ damage observed in MIS-C cases is directly caused by the virus, an abnormal immune response, or both (3).

In the literature, a study reported that non-thyroidal illness syndrome (NTIS) was common in cases of MIS-C. During severe acute illness, changes in thyroid hormones are termed NTIS and are characterized by a rapid decrease in serum triiodothyronine (T3) levels without an increase in thyroid stimulating hormone (TSH) levels (4).

In this study, we aimed to evaluate thyroid function tests in cases diagnosed with MIS-C, understand how the hypothalamus-pituitary-thyroid axis was affected, and investigate the relationship between disease severity and parameters of thyroid function.

Methods

Study Design and Definitions

This case-control study was conducted in the Department of the Pediatric Infectious Diseases, University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital in Turkey between January 2021 and September 2021.

The patient group consisted of MIS-C cases, aged between one month and 18 years, who met the MIS-C case definition according to the Centers for Disease Control and Prevention (CDC) report (5). The control group included healthy children without any known chronic disease.

Demographic characteristics, clinical findings, inflammatory markers, thyroid function tests, thyroid antibody levels, system involvement, treatments, and hospitalizations of MIS-C cases were recorded. Demographic data and thyroid function tests were recorded in the healthy control group. Thyroid function tests were evaluated before treatment in MIS-C cases. For both groups, patients with chronic disease, known thyroid dysfunction, and patients who were treated with steroids before diagnosis were excluded from the study.

The study protocol was approved by the Institutional Ethics Committee of University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital (decision no: 2021/06-33, date: 15.06.2021).

Thyroid Function Test Analysis

Clot activator tubes containing gel barrier (Vacutainer® SST II Advance tube, 5 mL, 13 x 100 mm; Becton Dickinson and Company, NJ, USA) were used for free triiodothyronine (fT3), free thyroxine (fT4), TSH, anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) antibody assays. Samples were quickly transferred to the laboratory. To separate the serum, SST II tubes were centrifuged at 1500 x g for 10 minutes. Serum fT3, fT4, TSH, anti-TPO, and anti-TG levels were determined using the chemiluminescence immunoassay method (UniCel DxI 800, Beckman Coulter, USA). Thyroid-stimulating hormone level was 0.34-5.76 mIU/L, anti-TPO antibody level was 0-10 IU/mL and anti-TG antibody level was 0-5 IU/mL in all age groups. Other thyroid function tests measurement levels varied according to age ranges. Normal ranges of fT3 were 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 fT4 normal range was 0.5-2.3 between one month and two years and 0.7-1.6 ng/dL between two and 18 years.

NTIS was defined as abnormal thyroid function tests seen in the presence of critical illness and the absence of a pre-existing abnormality in the hypothalamic-pituitary-thyroid axis (4). Thyroid function tests were measured prior to starting any steroid treatment.

Statistical Analysis

Statistical data were analyzed with IBM Statistical Package for the Social Sciences for Windows, version 25.0 (IBM Inc., Chicago, IL, USA). Values for numeric variables are given as median (interquartile range). Categorical variables were presented as numbers and percentages. Continuous variables following normal distribution were compared using a one-way analysis of variance or t-tests. The Mann-Whitney U test was used as a non-parametric test. Categorical variables were compared using the chi-square test. A p value of < 0.05 was considered statistically significant for all predictions.

Results

A total of 108 children were evaluated, 36 of them had MIS-C, meeting the CDC definition criteria, and 72 were

healthy. There was no statistically significant difference in terms of ages and gender ($p > 0.05$).

Clinical and Laboratory Findings in MIS-C Patients

Twenty-three (63.9%) MIS-C cases were male, 13 (36.1%) were female and their age was 98 ± 52 (53-136) months. In terms of MIS-C symptomology, all cases had fever. Other symptoms were: diarrhea in 22 (61.1%); nausea-vomiting in 19 (52.8%); abdominal pain in 13 (36.1%); rash in 11 (30.6%); cough in four (11.1%); headache in three (8.3%); myalgia in three (8.3%); mucositis in three (8.3%); sore throat in two (5.6%); dyspnea in one (2.8%); seizures in one (2.8%); and confusion in one (2.8%). In the medical histories, 26 (72.2%) MIS-C cases reported that they had contact with a SARS-CoV-2 positive case, confirmed by reverse transcription-polymerase chain reaction, in the four weeks preceeding onset of symptoms while five cases (13.9%) reported infection with SARS-CoV-2. In five (13.9%) cases, there was no history of contact or infection. Evidence of inflammation was found in laboratory tests of all MIS-C cases. Laboratory findings of the MIS-C cases, including inflammatory markers, are shown in Table 1. In terms of multi-organ involvement, system involvement of MIS-C cases was analyzed and hematological system involvement was found in all cases. Other systemic manifestations were: 35 (97.2%) gastrointestinal system; 14 (38.9%) cardiovascular system; 11 (30.6%) skin desquamation; four (11.1%) respiratory system; and two (5.6%) central nervous system involvement. Renal involvement was not observed in any of the cases. All patients received hydration and antibiotic therapy. Of the 27 (75%) who received steroid treatment, 25 (69.4%) received low-dose steroid (1-2 mg/kg/day), and two (5.6%) received pulse steroid treatment. When other treatment regimens were examined, intravenous immunoglobulin was administered in 26 (72.2%) cases, antithrombotic agents were administered in 25 (69.4%) cases, inotropic agents in five (13.9%) cases, and antiviral agents (favipiravir) in two (5.6%) cases. Only one (2.8%) case received immunomodulatory agent (anakinra) treatment. Plasmapheresis treatment was used in one of the cases (2.8%). While all patients were hospitalized, six (16.7%) patients were admitted to the intensive care unit (ICU). The median hospital stay was 8 (6-11) days, while the median ICU stay was 5 (3-7) days.

Changes in Thyroid Hormones

The median TSH value in the MIS-C group was 1.919 (1.12-2.577) mIU/L, and in the healthy group was 2.138 (1.571-3.004) mIU/L. The median fT3 level was 2.76 (2.485-3.31) ng/dL in the MIS-C group and 4.45 (4.07-4.79) ng/dL in the healthy group. The median fT4 level was 1.087 (0.976-1.203) ng/dL in the MIS-C group and 0.955 (0.855-1.065) ng/dL in the healthy group. When MIS-C and healthy control groups were compared in terms of thyroid hormones, median fT3 level was lower in MIS-C cases, while the median fT4 level was lower in the healthy group ($p < 0.001$ and $p = 0.001$, respectively).

When thyroid function tests were evaluated by reference intervals according to age, TSH level was within the normal range in all cases. However the fT3 level was low in 35 (97.2%) patients in the MIS-C group but was only low in four (5.6%) patients in the healthy group. The fT4 level was low in one (2.8%) patient in the MIS-C group and was also low in one (1.4%) patient in the healthy group. When both groups were compared, the fT3 level was lower in the MIS-C group ($p < 0.001$). Although the median fT4 level was significantly lower in the healthy group, no significant difference was found compared with the reference intervals according to age ($p = 0.318$).

Anti-TPO was positive in two (5.6%) cases, while anti-TG was positive in one (2.8%) case.

Clinical Comparison Between ICU and non-ICU Admission in MIS-C Patients

A total of six patients were admitted to the ICU. Five (83.3%) of them were male and their median age was 109 (85-168) months. When compared in terms of inflammatory markers, ferritin and D-dimer levels were higher in ICU admission ($p = 0.002$ and $p = 0.007$, respectively). As for thyroid function tests, fT3 level was lower in patients who were admitted to ICU ($p = 0.043$). Hypotension was found in five (83.3%) of the patients who were admitted to the ICU, and the presence of hypotension was found to be a significant finding in ICU admission ($p < 0.001$). ICU admission rates of cases with cardiovascular, skin, and respiratory system involvements were significantly higher ($p = 0.024$, $p = 0.006$ and $p = 0.010$, respectively). Similarly, use of inotropic therapy was also significantly more frequent in MIS-C cases requiring ICU admission ($p < 0.001$). The clinical comparison of MIS-C patients in terms of ICU admission is shown in Table 2.

Clinical Comparison Between Steroid and No Steroid Treatment in MIS-C Patients

In terms of symptoms, patients with vomiting and diarrhea were given steroid treatment more frequently ($p = 0.02$ and $p = 0.048$, respectively). Ferritin, D-dimer, and fibrinogen levels, which are acute phase inflammatory markers, were higher in MIS-C cases treated with steroids ($p < 0.001$, $p = 0.034$, $p = 0.007$, respectively). Conversely, fT3 levels

Table 1. Clinical and laboratory findings in MIS-C patients

	MIS-C group (n = 36)
Gender (male)*	23 (63.9)
Age (months)**	87 (53-136)
Clinical findings*	
Fever	36 (100)
Diarrhea	22 (61.1)
Nausea-vomiting	19 (52.8)
Abdominal pain	13 (36.1)
Rash	11 (30.6)
Cough	4 (11.1)
Headache	3 (8.3)
Myalgia	3 (8.3)
Laboratory findings	
Total WBC (10^3/uL)**	9.8 (7.8-16.4)
ALC (10^3/uL)***	1.1 (0.6-1.9)
C-reactive protein (mg/L)**	124.9 (63.7-189.2)
Procalcitonin (µg/L)***	0.98 (0.35-4.1)
Ferritin (ng/mL)**	145 (87-300)
D-dimer (µg/L)***	2020 (1240-3140)
Fibrinogen (mg/dL)**	481 (369-556)
Troponin I (ng/L)***	2.5 (2.5-17)
TSH (mIU/L)***	1.919 (1.12-2.577)
FT4 (ng/dL)**	1.087 (0.976-1.203)
FT3 (ng/dL)**	2.76 (2.485-3.31)
Anti-TG (IU/mL)***	0.9 (0.9-0.9)
Anti-TPO (IU/mL)***	0.4 (0.3-1.2)
System involvement*	
Hematological system	36 (100)
Gastrointestinal system	35 (97.2)
Cardiovascular system	14 (38.9)
Skin system	11 (30.6)
Respiratory system	4 (11.1)
Central nervous system	2 (5.6)
Treatment*	
Steroid	27 (75)
IVIg	26 (72.2)
Antithrombotic agent	25 (69.4)
Inotropic agent	5 (13.9)
Hospitalization*	36 (100)
Days of hospital stay**	8 (6-11)
ICU admission*	6 (16.7)
Days of ICU stay**	5 (3-7)

*n, % **mean ± SD ***median (IQR).
MIS-C: multisystem inflammatory syndrome in children, WBC: white blood cell, ALC: absolute lymphocyte count, TSH: thyroid stimulating hormone, FT3: free triiodothyronine, FT4: free thyroxine, ICU: intensive care unit, IQR: interquartile range, IVIg: intravenous immunoglobulin, SD: standard deviation, TG: thyroglobulin, TPO: thyroid peroxidase

were lower in cases requiring steroid treatment ($p < 0.001$). In terms of organ system involvement, only cardiovascular system involvement was seen more frequently in cases treated with steroids ($p = 0.048$). Duration of hospital stay was longer in patients treated with steroids ($p < 0.001$). The clinical comparison of MIS-C patients in terms of steroid treatment is shown in Table 3.

Discussion

Acute and chronic diseases can cause interactions of some neuroendocrine systems, including the hypothalamic-pituitary-thyroid axis (6). Data in the literature suggest that SARS-CoV-2 infection may have an effect on thyroid tissue and function (7). However, there are scarce data about MIS-C cases associated with SARS-CoV-2.

MIS-C is an immune-mediated phenomenon seen after acute infection. Cases with MIS-C present with single or multiple organ failure, manifested by fever, inflammation, cardiac dysfunction, hypotension, or life-threatening shock (8). Fever was present in all cases with MIS-C in the current study, and the most common organ involvements were the hematological and gastrointestinal systems. There are no data on endocrinological system involvement in MIS-C in current publications. This study was designed to investigate whether thyroid functions are affected in MIS-C cases.

There are some theories regarding hypothalamus-pituitary-thyroid axis abnormalities in COVID-19. The first of these is the appearance of TSH disorders through virus-associated hypophysitis. Another theory is that the thyroid gland is destructively damaged due to virus spread or excessive cytokine production. Finally, NTIS may be associated with severe disease states that are not specific to COVID-19 (9). Similar theories related to excessive cytokine formation and serious disease may be applicable in MIS-C cases. While NTIS was detected in 97.2% of our MIS-C cases, TSH abnormality was not detected in any of them. Since the number of participants was relatively small, it is not possible to exclude hypophysitis in this cohort of MIS-C cases. Thus, larger studies would be required to confirm this finding.

In NTIS, serum T3 level decreases rapidly from the onset of disease and this decrease is proportional to disease severity (10). NTIS typically occurs in critically ill patients and is closely associated with prognosis (11). This is considered a useful adaptation for conserving energy during critical illness (12). Similarly, in our study, fT3 levels were found to be lower in patients who were admitted to the ICU and who were severely unwell. In contrast, serum TSH levels of the participants remained within the normal range, suggesting that thyroidal T3 and T4 production was not greatly reduced.

Table 2. Clinical comparison between ICU and non-ICU admission in MIS-C patients

	ICU admission (n = 6)	Non-ICU admission (n = 30)	p
Gender (male)*	5 (83.3)	18 (60)	0.385
Age (months)**	109 (85-168)	82 (49-132)	0.259
Laboratory findings			
Total WBC (10^3/uL)**	9.8 (5-10.9)	10.5 (7.8-18.6)	0.140
ALC (10^3/uL)***	0.8 (0.4-1.4)	1.2 (0.6-2.5)	0.226
C-reactive protein (mg/L)**	159.1 (107-239.7)	112.7 (60.2-180.4)	0.379
Procalcitonin (µg/L)***	2.78 (0.46-5.94)	0.76 (0.31-4.07)	0.484
Ferritin (ng/mL)**	375 (270-450)	115 (79-223)	**0.002**
D-dimer (µg/L)***	3540 (3070-5400)	1575 (3184-5269)	**0.007**
Fibrinogen (mg/dL)**	519 (388-665)	454 (337-512)	0.340
Troponin I (ng/L)***	36.1 (2.8-82)	2.5 (2.5-3.94)	0.069
TSH (mIU/L)***	1.649 (1.508-2.281)	2.04 (1.085-2.683)	0.610
FT4 (ng/dL)**	1.207 (1.14-1.33)	1.039 (0.973-1.179)	0.273
FT3 (ng/dL)**	2.325 (1.95-2.89)	2.8 (2.58-3.49)	**0.043**
System involvement*			
Gastrointestinal system	6 (100)	29 (96.7)	1.000
Cardiovascular system	5 (83.3)	9 (30)	**0.024**
Skin system	5 (83.3)	6 (20)	**0.006**
Respiratory system	3 (50)	1 (3.3)	**0.010**
Central nervous system	0 (0)	2 (6.7)	1.000
Treatment*			
Steroid	6 (100)	21 (70)	0.303
IVIg	6 (100)	20 (66.7)	0.157
Antithrombotic agent	6 (100)	19 (68.3)	0.148
Inotropic agent	5 (83.3)	0 (0)	**< 0.001**

*n, % **mean ± SD ***median (IQR).
ICU: intensive care unit, MIS-C: multisystem inflammatory syndrome in children, WBC: white blood cell, ALC: absolute lymphocyte count, TSH: thyroid stimulating hormone, FT3: free triiodothyronine, FT4: free thyroxine, IQR: interquartile range, IVIg: intravenous immunoglobulin, SD: standard deviation

In a study of patients with sepsis presenting with NTIS, patients with combined low T3 and T4 levels had a worse prognosis than those with low T3 alone (13). In our study, combined low T3 and T4 levels were detected in only one case in the MIS-C group, so it is not possible to reliably comment on this issue.

In the literature, there are studies examining thyroid antibody status, including adult patient populations. In a study conducted in India, anti-TPO seropositivity was found in 13.6% of the participants (14). In a study involving a large number of cases in the European population, 23.6% of participants without known thyroid disease were found to be seropositive for at least one thyroid autoantibody (15). In our study, anti-TPO seropositivity was found in 5.6% of MISC cases. The participants' pre-MIS-C thyroid antibody status was unknown; however, it is thought that thyroid autoimmunity may be triggered in some MIS-C cases. Therefore, it may be important to monitor MIS-C patients for thyroid autoantibody development.

Study Limitations

Our study had some limitations. Due to the relatively small number of participants and the lack of follow-up of patients' thyroid function parameters, more studies are needed to confirm our data.

Conclusion

In conclusion, since the endocrine system critically coordinates and regulates important metabolic and biochemical pathways, investigation of endocrine functions may be beneficial in MIS-C. In our study, low fT3 levels were associated with both the diagnosis of MIS-C and requirement for ICU admission. To the best of our knowledge, there is only one study addressing this issue (4). Further studies are needed to predict the prognosis and develop a long-term follow-up management plan.

Table 3. Clinical comparison between steroid and no steroid treatment in MIS-C patients

	Steroid treatment (n = 27)	No steroid treatment (n = 9)	p
Gender (male)*	16 (59.3)	7 (77.8)	0.317
Age (months)**	85 (49-140)	96 (67-126)	0.881
Laboratory findings			
Total WBC (10^3/uL)**	9.7 (7.4-16.5)	11.3 (7.8-16.2)	0.950
ALC (10^3/uL)***	1.3 (0.6-1.9)	1 (0.6-1.6)	0.522
C-reactive protein (mg/L)**	135 (68.6-208.9)	73 (54.1-137.7)	0.093
Procalcitonin (µg/L)***	1.55 (0.38-4.07)	0.46 (0.12-5.69)	0.622
Ferritin (ng/mL)**	201 (113-400)	81 (49-110)	**< 0.001**
D-dimer (µg/L)***	2180 (1440-3870)	1310 (1110-1850)	**0.034**
Fibrinogen (mg/dL)**	504 (388-621)	337 (243-454)	**0.007**
Troponin I (ng/L)***	2.7 (2.5-20.3)	2.5 (2.5-2.5)	0.113
TSH (mIU/L)***	1.707 (1.085-2.351)	2.397 (2.021-2.683)	0.315
fT4 (ng/dL)**	1.03 (0.947-1.204)	1.105 (1.047-1.172)	0.645
fT3 (ng/dL)**	2.66 (2.31-3.02)	3.55 (3.29-3.98)	**< 0.001**
System involvement*			
Gastrointestinal system	26 (96.3)	9 (100)	1.000
Cardiovascular system	13 (48.1)	1 (11.1)	**0.048**
Skin system	10 (37)	1 (11.1)	0.144
Respiratory system	4 (14.8)	0 (0)	0.553
Central nervous system	1 (3.7)	1 (11.1)	0.443
Days of hospital stay**	9 (7-12)	4 (4-6)	**< 0.001**

*n, % **mean ± SD ***median (IQR).
MIS-C: multisystem inflammatory syndrome in children, WBC: white blood cell, ALC: absolute lymphocyte count, TSH: thyroid stimulating hormone, FT3: free triiodothyronine, FT4: free thyroxine, IQR: interquartile range, SD: standard deviation

Ethics

Ethics Committee Approval: The study protocol was approved by the Institutional Ethics Committee of University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital (decision no: 2021/06-33, date: 15.06.2021).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Gönül Çatlı, Concept: Ayşegül Elvan-Tüz, İlkay Ayrancı, Eda Karadağ-Öncel, Bumin Nuri Dündar, Design: Gönül Çatlı, Ahu Kara-Aksay, Eda Karadağ-Öncel, Bumin Nuri Dündar, Data Collection or Processing: İlkay Ayrancı, Analysis or Interpretation: Ahu Kara-Aksay, Dilek Yılmaz, Literature Search: Ayşegül Elvan-Tüz, Yıldız Ekemen-Keleş, İnanç Karakoyun, Writing: Ayşegül Elvan-Tüz.

Financial Disclosure: The authors declared that this study received no financial support.

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