EXPERIMENTAL WORKS

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SARS-CoV-2 INFECTION AND THYROID DYSFUNCTION IN CHILDREN

K. V. KOZAK[1]✉, H. A. PAVLYSHYN[1], I. Y. AVRAMENKO[2], O. M. DYVONYAK[3], O. O.SHEVCHUK[1], K. T. HLUSHKO[1]

[1]I. Horbachevsky Ternopil National Medical University, Ternopil, Ukraine;
[2]Danylo Halytsky Lviv National Medical University, Lviv, Ukraine;
[3]Ternopil Municipal Children's Hospital, Ternopil, Ukraine;
✉e-mail: kozakk@tdmu.edu.ua

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The problem of thyroid dysfunction related to SARS-CoV-2 infection remains unclear in children. Therefore, the study aimed to reveal the interrelationship between thyroid dysfunction and COVID-19 severity as well as to determine optimal cut-off values for screening for thyroid disorders in children. A total number of 90 children aged from 1 month to 17 years were involved in the study. Patients with known thyroid disease were not recruited for the research. A thyroid panel was assessed for all participants that included: free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH) and anti-thyroid peroxidase (ATPO) antibodies. Statistical analysis was done using the computer software Statistica 13.0. Research has revealed euthyroid sick syndrome (ESS) in 14.10% of SARS-CoV-2 infected children more often among patients with severe COVID-19 and multisystem inflammatory syndrome (33.33%) compared to mild COVID-19 course (6.67%) and moderate disease severity (8.89%) ($P < 0.05$). Significant correlation relationships were revealed for next values – FT3 and erythrocyte sedimentation rate (ESR) ($r_s = -0.22$; $P < 0.05$); FT3 and C-reactive protein (CRP) ($r_s = -0.33$; $P < 0.05$); FT3 and procalcitonin ($r_s = -0.43$; $P < 0.05$). The next cut-off values for ESS determination were revealed: ESR 18.5 mm/h (AUC 0.803); CRP 11.5 mg/l (AUC 0.763); ferritin 84.8 ng/ml (AUC 0.733). Results suggest that pediatricians should pay attention to the endocrine disruptions by COVID-19 in children.

K e y w o r d s: COVID-19, euthyroid sick syndrome in children, inflammatory markers.

COVID-19 in childhood, as well as in adulthood, has a different course and outcomes. Systemic manifestations of SARS-CoV-2 vary, and thyroid dysfunction is among them [1, 2]. Previous research in adults suggests that the incidence of thyroid gland disorders varies from 13 to 64% [3]. Notably, the thyroid gland, pituitary gland and hypothalamus have high expression of angiotensin-converting enzyme 2 receptor in their cells, which contributes significantly to the SARS-CoV-2 penetration and further cell damage [2, 4]. Most commonly, SARS-CoV-2 infection is related to euthyroid sick syndrome (ESS) in childhood, which also can be called nonthyroidal illness syndrome or low triiodothyronine (T3) illness [1, 3, 4]. The key marker of ESS is a predominantly low T3

level, and decreased thyroxine (T4) or thyroid-stimulating hormone (TSH), also called thyrotropin, can be revealed. At the same time, reports underlined the increased frequency of subacute thyroiditis and thyrotoxicosis [4, 5].

Recent studies suggest that ESS appears in the case of systemic diseases such as SARS-CoV-2 infection to protect tissues from ongoing damage and energy deficiency [1]. It is especially important in the case of severe disease course. Current data suggest that in the case of COVID-19, activity of type 3 deiodinase (DIO3) increases. The role of DIO3 is to convert T3 and T4 in the 3,3-T2 and reverse T3, respectively [1]. It also must be underlined that systemic illness can be associated with impaired function of type 1 (DIO1) and type 2 deiodinase (DIO2), which helps to make active hormone T3 from nonactive T4 [1, 6]. The research underlines the importance of thyroid hormones in the maintenance of immune response – T-cell immunity and interferon response [4]. At the same time, thyroid hormone levels are crucial for maintaining normal organism functioning during serious illness. Simultaneously, coronavirus infection leads to the cytokine storm and intensive inflammatory response, which aggravates thyroid function. Therefore, we have interchangeable influence – coronavirus disease's influence on thyroid function and thyroid function predicting further COVID-19 clinical course.

Recent studies underlined the association between low thyroid hormones levels, especially FT3, and critical disease as well as increased mortality related to SARS-CoV-2 infection [7]. Despite the presence of much research on adults [5, 8], it remains unclear in the pediatric population. A routine thyroid panel study is not indicated for asymptomatic patients with COVID-19. As a result, timely diagnosis of thyroid dysfunction in children with SARS-CoV-2 isn't made. Therefore, the study aimed to reveal the interrelationship between thyroid dysfunction related to COVID-19 and the clinical course of the coronavirus disease in addition to determining prognostic cut-off values for ESS prediction based on the pro-inflammatory markers' levels (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), procalcitonin and ferritin).

Materials and Methods

A total of 90 children aged 1 month to 17 years were involved in the study; the average age was (6.07 ± 5.07) years. There were 59 boys (65.56%) and 31 girls (34.44%).

Among the study group, 78 patients (86.67%) had confirmed SARS-CoV-2 infection and 12 children (13.33%) were noninfected (PCR negative and IgG negative).

According to disease severity, all patients were divided into three study groups: 1) 15 children (19.23%) with mild COVID-19 severity; 2) 45 patients (57.69%) with moderate disease severity; 3) 18 patients (23.08%) with severe COVID-19 and multisystem inflammatory syndrome in children (MIS-C).

Disease severity was defined using criteria of the Italian Society of Pediatric Infectious Disease [9, 10] and COVID-19 Treatment Guidelines (National Institutes of Health) [11]. Mild cases were defined as cases when patients had upper airway symptoms without radiological/ultrasound findings, children were febrile or afebrile. Moderate disease severity was diagnosed in cases when pneumonia was detected with imaging studies or upper airway symptoms were accompanied by respiratory distress. Severe disease was noted when patients had fever or cough with one of the following: oxygen saturation <92% on room air, severe respiratory distress or systemic symptoms (drowsiness, lethargy, seizures, dehydration). MIS-C was defined according to World Health Organization criteria [12]. Patients with severe COVID-19 and MIS-C received low-dose corticosteroids (methylprednisolone 1-2 mg/kg/day in two divided doses or dexamethasone 6 mg/day) for three to five days. Five patients with MIS-C had a single infusion of intravenous immune globulin (IVIG) in the dosage of 2 mg/kg and for one patient IVIG was given twice.

Patients with known thyroid disease were not recruited for the research. Informed consent was obtained from all participants (all caregivers). The study was done according to the Declaration of Helsinki, 2013. The Bioethics Commission of the I. Horbachevsky Ternopil National Medical University (Protocol № 59 from June 05, 2020) approved the study.

A thyroid panel was assessed for all children. The following kits for enzyme immunoassay were used: Free Triiodothyronine (FT3) Test System (Monobind, USA), Free Thyroxine (FT4) Test System (Monobind, USA), Thyrotropin (TSH) Test System (Monobind, USA) and Anti-thyroid peroxidase (ATPO) antibodies (DiaMetra, Immunodiagnostic Systems Holdings Ltd., UK). Based on kit instructions, we used the following normal values for research parameters: FT3 – 1.4–4.2 pg/ml; FT4 –

0.8–2.0 ng/dl; TSH – 0.53–5.60 μIU/ml; ATPO – <20 IU/ml. ESS was defined in the case when deviations in the thyroid hormonal panel were revealed.

The following kits were used to assess proinflammatory markers: Human PCT (Procalcitonin) ELISA Kit (Elabscience, USA); Human CRP (C-Reactive Protein) ELISA Kit (Elabscience, USA); Ferritin AccuBind VAST ELISA Kits (Monobind Inc., USA).

All parameters were assessed in the serum. Blood samples were taken during the first 48 h after hospital admission.

Statistical analysis was done using the computer Statistica 13.0 software (StatSoft Inc., Tulsa, Oklahoma, USA). The Mann-Whitney test was used for the comparison of two independent samples. A comparison of four groups was made with the Kruskal-Wallis test. Frequency tables were analyzed with the Pearson Chi-square test. Spearman rank correlation was done to assess the relationship between qualitative values. We used ROC analysis as a diagnostic tool to determine cut-off values. The level of statistical significance was assumed in the case of $P < 0.05$.

Results

Patients with different COVID-19 severity and healthy children didn't have significant differences in their TSH levels ($P > 0.05$). Concomitantly, patients with severe coronavirus infection as well as children with MIS-C had lower levels of FT3 and FT4 compared to noninfected persons. Increased disease severity was notably associated with lower thyroid hormone levels (Table 1). ATPO level was significantly higher in patients with severe COVID-19 courses compared to the patients with mild and moderate disease severities (Table 1).

Noninfected children had normal levels of TSH, FT3, FT4 and ATPO (Table 2). Meanwhile, in the group of children who were infected with SARS-CoV-2, we have revealed the next deviations: abnormal (elevated or low) TSH level was registered in 10.25% of children, low FT3 level in 10.25% of all infected persons, low FT4 in 6.41% of children and elevated ATPO in 15.38% of cases. Notably, low FT3 levels as well as elevated ATPO levels were seen significantly more often among children with severe COVID-19 and MIS-C compared to other studied groups ($P < 0.001$) (Table 2).

Research revealed ESS in 14.10% of SARS-CoV-2 infected children. Notably, ESS was revealed significantly more often among patients with severe COVID-19 and MIS-C (33.33%) compared to patients with mild COVID-19 course (6.67%) and moderate disease severity (8.89%) ($\chi = 10.05$;

Table 1. Level of TSH, FT3, FT4, ATPO in children with COVID-19

Parameter		Disease severity			Control group (4)
		Mild (1)	Moderate (2)	Severe + MIS-C (3)	
TSH	level, μIU/ml	1.54 (1.21; 2.98)	1.53 (1.05; 3.01)	2.71 (1.02; 4.19)	1.77 (1.41; 3.03)
	H; *P*	H = 1.60; *P* = 0.660			
	P-value	$P_{1\text{-}2,\ 1\text{-}3,\ 1\text{-}4,\ 2\text{-}3,\ 2\text{-}4,\ 3\text{-}4} > 0.05$			
FT3	level, pg/ml	3.97 (3.13; 4.34)	3.45 (3.02; 4.03)	2.54 (1.33; 3.38)	3.79 (3.46; 4.13)
	H; *P*	H = 17.95; *P* < 0.001*			
	P-value	$P_{1\text{-}2,\ 1\text{-}4,\ 2\text{-}4 > 0.05;\ p1\text{-}3,\ 2\text{-}3,\ 3\text{-}4} < 0.05$*			
FT4	level, ng/dl	1.41 (1.28; 1.56)	1.35 (1.26; 1.48)	1.36 (1.06; 1.47)	1.55 (1.47; 1.64)
	H; *P*	H = 10.18; *P* = 0.017*			
	P-value	$P_{1\text{-}2,\ 1\text{-}3,\ 1\text{-}4,\ 2\text{-}3} > 0.05$; $P_{2\text{-}4,\ 3\text{-}4} < 0.05$*			
ATPO	level, IU/ml	1.77 (1.39; 2.60)	1.87 (1.38; 2.27)	23.43 (2.13; 53.02)	2.55 (1.58; 3.44)
	H; *P*	H = 13.82; *P* = 0.003*			
	P-value	$P_{1\text{-}2,\ 1\text{-}4,\ 2\text{-}4,\ 3\text{-}4} > 0.05$; $P_{1\text{-}3,\ 2\text{-}3} < 0.05$*			

Note. 1. TSH – Thyroid-stimulating hormone; FT3 – Free Triiodothyronine; FT4 – Free Thyroxine; ATPO – Antithyroid peroxidase antibodies. 2. H – Kruskal-Wallis test; *P* – level of its significance. 3. *P*-values – level of statistical significance for multiple comparisons. 4. *Statistically significant result ($P < 0.05$)

Table 2. Results of thyroid function test in children with different COVID-19 disease severity and healthy children, n (%)

Parameter		Disease severity			Control group	χ^2; *P*
		Mild	Moderate	Severe + MIS-C		
TSH	Normal	14 (93.33%)	39 (86.67%)	17 (94.44%)	12 (100.00%)	$\chi^2 = 3.40$; $P = 0.757$
	Elevated	0 (0.00%)	2 (4.44%)	0 (0.00%)	0 (0.00%)	
	Low	1 (6.67%)	4 (8.89%)	1 (5.56%)	0 (0.00%)	
FT3	Normal	5 (100.00%)	43 (95.56%)	12 (66.67%)	12 (100.00%)	$\chi^2 = 17.01$; $P < 0.001$*
	Low	10 (0.00%)	2 (4.44%)	6 (33.33%)	0 (0.00%)	
FT4	Normal	14 (93.33%)	43 (95.56%)	16 (88.89%)	12 (100.00%)	$\chi^2 = 1.91$; $P = 0.592$
	Low	1 (6.67%)	2 (4.44%)	2 (11.11%)	0 (0.00%)	
ATPO	Normal	15 (100.00%)	43 (95.56%)	8 (44.44%)	12 (100.00%)	$\chi^2 = 35.00$; $P < 0.001$*
	Elevated	0 (0.00%)	2 (4.44%)	10 (55.56%)	0 (0.00%)	

Note. 1. TSH – Thyroid-stimulating hormone; FT3 – Free Triiodothyronine; FT4 – Free Thyroxine; ATPO – Anti-thyroid peroxidase antibodies. 2. χ^2 – Pearson Chi-square test; *P* – level of its significance. 3. *Statistically significant result ($P < 0.05$)

Table 3. Frequency of ESS among children with COVID-19 and noninfected children

Parameter		Disease severity			Control group	χ^2; *P*
		Mild	Moderate	Severe + MIS-C		
Euthyroid sick syndrome	absent	14 (93.33%)	41 (91.11%)	12 (66.67%)	12 (100.00%)	$\chi^2 = 10.05$; $P = 0.018$*
	present	1 (6.67%)	4 (8.89%)	6 (33.33%)	0 (0.00%)	

Note 1. χ^2 – Pearson Chi-square test; p – level of its significance. 2. *Statistically significant result ($P < 0.05$)

$P = 0.018$). At the same time, patients from the control group (noninfected persons) didn't have any thyroid dysfunction (Table 3).

Our data confirmed that disease severity is associated with higher values of pro-inflammatory markers. Patients with moderate and severe SARS-CoV-2 had higher ESR, CRP, procalcitonin and ferritin than noninfected persons (Table 4). It must be emphasized that levels of ESR, procalcitonin and ferritin didn't differ significantly between children with mild COVID-19 course and healthy children; only CRP was higher in the case of even mild coronavirus infection compared to noninfected persons (Table 4). At the same time, pro-inflammatory markers in the case of mild and moderate COVID-19 severity were not significantly different ($P > 0.05$) (Table 4).

Patients with higher proinflammatory markers had lower FT3 levels. Significant correlation relationships were revealed for the next values – FT3 and ESR ($r_s = -0.22$; $P < 0.05$); FT3 and CRP ($r_s = -0.33$; $P < 0.05$); FT3 and procalcitonin ($r_s = -0.43$; $P < 0.05$) (Table 5).

Considering observed correlations, we have revealed that COVID-19 patients with ESS had significantly higher levels of ESR and CRP compared to those with COVID-19 but without thyroid disorders (Table 6).

Results have shown that higher levels of proinflammatory markers are associated with an increased risk of thyroid dysfunction in the case of COVID-19 in children. Therefore, we conducted ROC analysis to determine prognostic values of ESR, CRP, procalcitonin and ferritin for ESS diagnosis. The level of ESR higher than 18.5 mm/h with a sensitivity of 0.82 and specificity of 0.69 can predict ESS appearance ($P < 0.001$). The optimal cut-off point for CRP in ESS prediction was 11.5 mg/l area under the curve (AUC) 0.763; $P < 0.05$. At the same time, a ferri-

Table 4. Levels of proinflammatory markers in children with different COVID-19 severity

Parameter		Disease severity			Control group	H; *P*
		Mild	Moderate	Severe + MIS-C		
ESR	level, mm/h	14.0 (10.0; 16.0)	17.0 (6.0; 23.0)	24.0 (20.0; 42.0)	7.5 (5.0; 9.0)	$\chi^2 = 38.43$; $P < 0.001$*
	P-values	$P_{1\text{-}2,\ 1\text{-}4} > 0.05$; $P_{1\text{-}3,\ 2\text{-}3,\ 2\text{-}4,\ 3\text{-}4} < 0.05$*				
CRP	level, mg/l	6.19 (3.08; 13.30)	11.09 (6.00; 24.00)	15.50 (11.46; 95.70)	1.08 (0.98; 2.00)	$\chi^2 = 32.27$; $P < 0.001$*
	P-values	$P_{1\text{-}2,\ 2\text{-}3} > 0.05$; $P_{1\text{-}3,\ 1\text{-}4,\ 2\text{-}4,\ 3\text{-}4} < 0.05$*				
Procalcitonin	level, pg/ml	168.90 (60.13; 340.00)	236.42 (104.50; 469.50)	1190.00 (334.70; 4900.70)	31.87 (20.64; 40.48)	$\chi^2 = 28.42$; $P < 0.001$*
	P-values	$P_{1\text{-}2,\ 1\text{-}4} > 0.05$; $P_{1\text{-}3,\ 2\text{-}3,\ 2\text{-}4,\ 3\text{-}4} < 0.05$*				
Ferritin	level, ng/ml	67.36 (48.39; 134.70)	87.71 (29.43; 126.34)	137.10 (90.90; 390.10)	48.35 (37.26; 66.55)	$\chi^2 = 11.07$; $P < 0.05$*
	P-values	$P_{1\text{-}2,\ 1\text{-}3,\ 1\text{-}4,\ 2\text{-}4} > 0.05$; $P_{2\text{-}3,\ 3\text{-}4} < 0.05$*				

Note 1. ESR – erythrocyte sedimentation rate; CRP – C-reactive protein. 2. H − Kruskal-Wallis test; *P* – level of its significance. 3. *P*-values − level of statistical significance for multiple comparisons. 4. *Statistically significant result ($P < 0.05$)

Table 5. Intercorrelations between inflammatory markers and thyroid hormones

Parameter	ESR	CRP	Procalcitonin	Ferritin
TSH	$r = 0.04$	$r = 0.01$	$r = 0.05$	$r = 0.07$
FT3	$r = -0.22$*	$r = -0.33$*	$r = -0.43$*	$r = -0.07$
FT4	$r = -0.16$	$r = -0.19$	$r = -0.26$	$r = -0.13$
ATPO	$r = 0.08$	$r = 0.05$	$r = 0.14$	$r = -0.01$

Note. 1. TSH − Thyroid-stimulating hormone; FT3 − Free Triiodothyronine; FT4 − Free Thyroxine; ATPO − Anti-thyroid peroxidase antibodies; ESR – erythrocyte sedimentation rate; CRP – C-reactive protein. 2. *r* − Spearman rank correlation. 3. *Statistically significant result ($P < 0.05$)

Table 6. Inflammatory markers in patients with ESS

Parameter		ESR, mm/h	CRP, mg/l	Procalcitonin, pg/ml	Ferritin, ng/ml
Euthyroid sick syndrome	absent	14.00 (8.00; 23.00)	9.67 (4.46; 13.78)	217.80 (60.13; 580.00)	77.18 (33.21; 134.90)
	present	25.00* (20.00; 40.00)	27.56* (11.77; 96.00)	545.25 (145.33; 5000.20)	134.70 (66.74; 390.10)

Note. 1. ESR – erythrocyte sedimentation rate; CRP – C-reactive protein. 2. *Statistically significant difference ($P < 0.05$)

tin level higher than 84.8 ng/ml was related to ESS development in pediatric COVID-19 patients (AUC 0.733). Only for procalcitonin, AUC was 0.682, which was below the level of statistical significance $P > 0.05$ (sensitivity 0.60; specificity 0.58) (Table 7, Fig.).

Discussion

The frequency of ESS in our pediatric population corresponds to the data in adults – 14.1% in our study compared to 7.9−14.5% in adults [2, 13, 14]. However, other data underlined a higher frequency

Table 7. Role of ESR, CRP and procalcitonin levels in the prediction of euthyroid sick syndrome

Parameter	ESR	CRP	Procalcitonin	Ferritin
AUC	0.803	0.763	0.682	0.733
95% CI AUC	0.687–0.918	0.613–0.913	0.485–0.879	0.584–0.882
P	0.001*	0.007*	0.074	0.025*
Cut-off value	18.5	11.5	277.1	84.8
Sensitivity	0.818	0.800	0.600	0.889
Specificity	0.691	0.586	0.578	0.532

Note. 1. ESR – erythrocyte sedimentation rate; CRP – C-reactive protein. 2. AUC – area under curve; 95% CI AUC – 95% confidence interval for area under curve. 3. *Statistically significant result ($P < 0.05$)

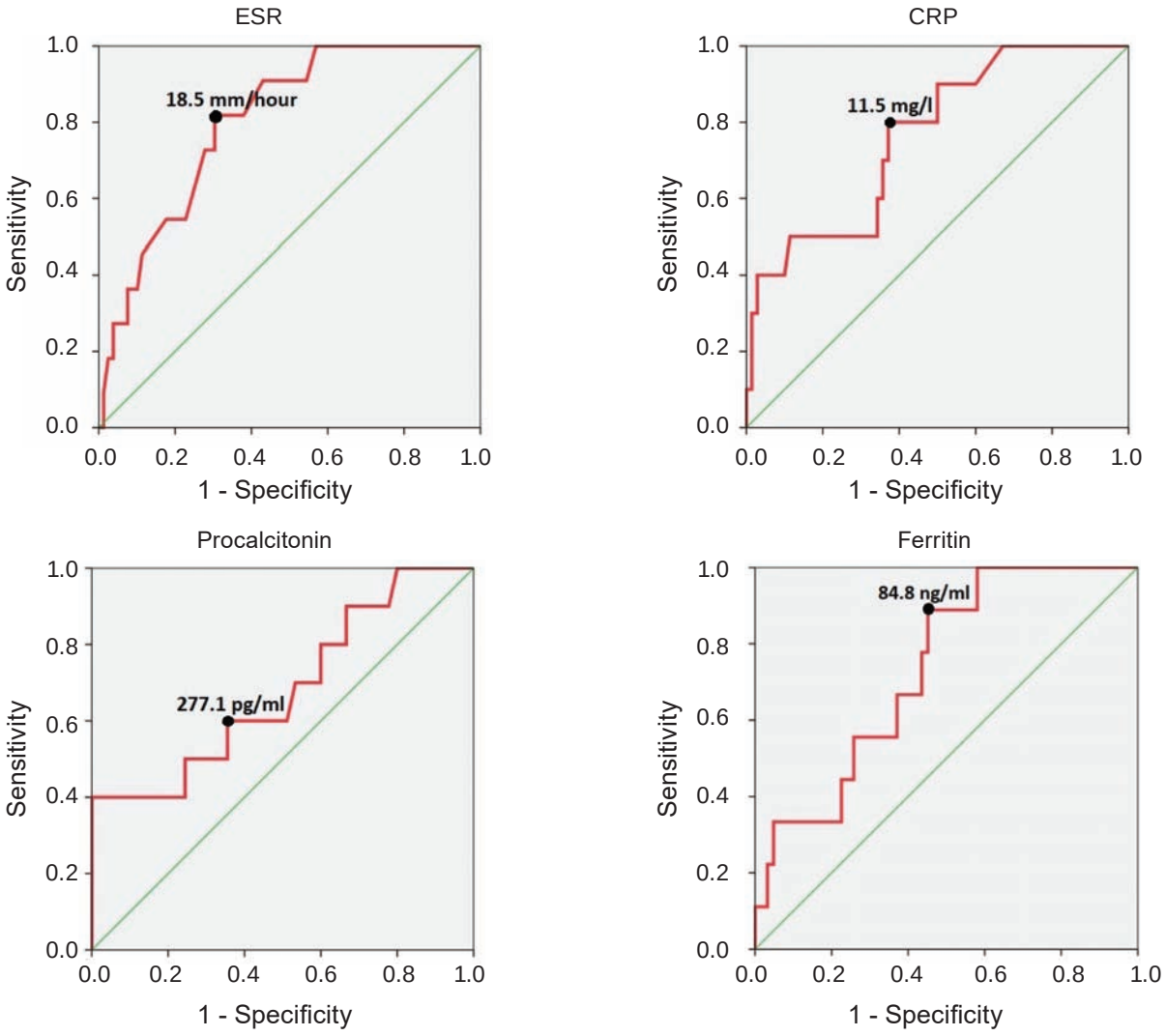

Fig. ROC-curves for the prediction of ESS in children with COVID-19

of ESS in the adult population – 27.52% [7]. Notably, ESS was revealed significantly more often among patients with severe COVID-19 and MIS-C compared to patients with mild and moderate disease courses. In our research, the frequency of ESS among patients with severe MIS-C and severe COVID-19 was lower compared to the study when ESS was assessed only in children with MIS-C – 33.3 and 88.4%, respectively [15]. For adults, the same patterns in ESS frequency were typical – patients with the critical disease were more prone to have low FT3 and TSH levels [16].

Analyses of thyroid hormones levels in our study correspond to the data obtained by other researchers. The most common finding typical for children with severe COVID-19 and MIS-C is a low FT3 level [15]. At the same time, low FT4 level was seen in 11% of severe cases, while in other studies it was 27% [15]. Notably, deviations in TSH level were not so frequent in our study (5.6%) and in the study of Italian researchers (7.8%) [15]. Subclinical hypothyroidism was revealed in 4.44% of pediatric patients with SARS-CoV-2, while in adults it was registered two times more often – in 7.23% infected persons [2].

In addition, COVID-19 can lead to subacute thyroiditis or autoimmune thyroiditis. Autoimmune thyroiditis in the case of SARS-CoV-2 infection can occur due to the misbalanced of T helper type 1 and type 2 immune responses as well as the results of cytokine activation [17, 18]. Some researchers underlined that it is a strict relationship to molecular mimicry in the case of coronavirus infection – antibodies against SARS-CoV-2 can react with thyroid peroxidase [19]. Autoimmune thyroiditis in our research was asymptomatic. Such clinical course can be explained by lymphocytopenia and, as a result, reduced lympho-phagocytic infiltration of the thyroid tissue and absence of pain [17].

The interrelationship between thyroid hormone secretion and COVID-19 has different pathophysiological influences. Thyroid cells have high expression of angiotensin converting enzyme 2 and, therefore, could be the target cell for the SARS-CoV-2 virus. The last fact is related to the direct cytotoxic effect on the thyroid and primary thyroid dysfunction. Direct thyroid follicular damage can be caused by the apoptosis induced by SARS-CoV-2 [20]. Along with this, thyroid gland can be affected by the increased interleukin production, the so-called "cytokine storm" [15]. Based on current studies, few proinflammatory cytokines are involved in the pathogenesis of ESS – interleukin-1 beta (IL-1 β), tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6) and interferon gamma (IFN-γ) [1]. Most of them (IL-1β, TNF-α, IL-6) decrease iodine uptake and decrease the activity of DIO1 (IL-1β, IL-6, IFN-γ), at the same time IL-6 enhances 5-deiodinase activity [1, 7]. IL-1β and TNF-α can also lead to secondary thyroid dysfunction through the direct influence on the pituitary gland [1]. It should be noticed that a high interleukins level is associated with a high level of inflammatory markers [7].

The high frequency of ESS among children with severe COVID-19 and MIS-C can be also explained by the approach to the management of these clinical forms of SARS-CoV-2 infection. Patients involved in our study didn't receive high dosages of glucocorticoid therapy – only low-dosage therapy with a short duration. Meanwhile, glucocorticoids have a negative effect on the thyrotropin-releasing hormone and, as a result, suppress the secretion of TSH. At the same time, these drugs influence the FT4-FT3 conversion through the stimulation of DIO3 [1, 7]. Glucocorticoids have a negative impact on the thyroid-binding globulin and decrease the intake of T4 by peripheral tissues [7, 21].

It must be emphasized that studies have shown that patients with low FT3 are at greater risk for negative outcomes in the case of COVID-19 compared to patients with normal thyroid profiles [21]. But still, the explanation for this finding is unknown and widely discussed among scientists [22]. Nevertheless, studies continue in order to improve outcomes based on the revealed features. One of the strategies to deal with the severe COVID-19 course as well as negative early and late outcomes is to include T3 in the management of COVID-19 [22]. Still now, research is ongoing. However, in children, we don't have such studies. Also worldwide, the assessment of thyroid profile has not been the focus of clinicians and is not emphasized by any disease-related recommendation. Therefore, it is obvious to find a risk group for ESS development among pediatric COVID-19 patients. It can be a helpful tool to manage these patients correctly and provide in-time correction to improve outcomes and patients' quality of life.

Our research revealed a negative correlation between proinflammatory markers and thyroid hormones levels that corresponds to the study of other colleagues [7, 20, 21, 23]. Despite this, such find-

ings didn't have any next evaluation. No diagnostic markers for ESS prediction were identified, especially in the pediatric population for whom a normal thyroid profile is crucial for maintaining normal growth and development. These new results were obtained in our study. It was revealed that elevated levels of ESR (≥18.5 mm/hour), CRP (≥11.5 mg/l), procalcitonin (≥277.1 pg/ml) and ferritin (≥84.8 ng/ml) are related to ESS development in pediatric patients with COVID-19. These findings can be a helpful tool to suspect thyroid gland disorders in clinical settings during the management of different severity of COVID-19 in children.

Conclusion. From 6.7% to 33.3% of pediatric patients with COVID-19 had ESS; frequency significantly increases with the increase of disease severity. At the same time, children with thyroid dysfunction had higher levels of pro-inflammatory markers, which were in the inverse correlation with FT3. The study revealed prognostic cut-off values for ESS prediction in children suffering from COVID-19. These values of proinflammatory markers must increase the awareness of clinicians on thyroid dysfunction: ESR – 18.5 mm/h; CRP – 11.5 mg/l; ferritin – 84.8 ng/ml.

The problem of thyroid dysfunction must be considered not only by researchers and endocrinology subspecialists but also by pediatricians and infectious specialists. Timely diagnosis and monitoring of possible disorders can prevent adverse late outcomes.

Conflict of interest. Authors have completed the Unified Conflicts of Interest form at http://ukrbiochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

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ІНФЕКЦІЯ SARS-CoV-2 ТА ТИРЕОЇДНА ДИСФУНКЦІЯ У ДІТЕЙ

К. В. Козак[1]✉, Г. А. Павлишин[1], І. Ю. Авраменко[2], О. М. Дивоняк[3], О. О. Шевчук[1], К. Т. Глушко[1]

[1]Тернопільський національний медичний університет ім. І. Я. Горбачевського МОЗ України, Тернопіль, Україна;
[2]Львівський національний медичний університет імені Данила Галицького, Львів, Україна;
[3]Комунальне некомерційне підприємство «Тернопільська міська дитяча комунальна лікарня», Тернопіль, Україна;
✉e-mail: kozakk@tdmu.edu.ua

Проблема дисфункції щитовидної залози, пов'язаної з інфекцією SARS-CoV-2, залишається невирішеною в педіатричній практиці. Метою дослідження було виявити взаємозв'язок між дисфункцією щитовидної залози у дітей з COVID-19, та клінічним перебігом коронавірусної хвороби, а також з'ясувати прогностичні маркери асоційовані із виникненням цієї дисфункції. У дослідженні взяли участь 90 дітей віком від 1 місяця до 17 років. Пацієнти, у яких в анамнезі були захворювання щитовидної залози не брали участь у дослідженні. Для всіх учасників оцінювали панель щитовидної залози: вільний трийодтиронін (вТ3), вільний тироксин (вТ4), тиреотропний гормон (ТТГ), антитіла до тиреоїдної пероксидази (АТПО). Статистичний аналіз проводили за допомогою комп'ютерного програмного забезпечення «Statistica 13.0». Дисфункцію щитоподібної залози виявлено у 14.10 % дітей, інфікованих SARS-CoV-2, значно частіше серед пацієнтів із тяжким перебігом COVID-19 та MIS-C (33,33%) порівняно з легким перебігом COVID-19 (6,67%) та середнім ступенем тяжкості захворювання (8,89%) ($P < 0,05$). Достовірні кореляційні зв'язки виявлені для наступних значень – вТ3 та ШОЕ ($r_s = -0,22$; $P < 0,05$); вТ3 і С-реактивний протеїн ($r_s = -0,33$; $P < 0,05$); вТ3

і прокальцитонін (r_s = -0,43; P < 0,05). Виявлено наступні порогові значення прозапальних маркерів задля діагностики дисфукції щитоподібної залози: ШОЕ 18,5 мм/год (AUC 0,803); С-реактивний протеїн 11,5 мг/л (AUC 0,763); феритин 84,8 нг/мл (AUC 0,733). Враховуючи отримані дані, необхідно підкреслити доцільність моніторингу ендокринних порушень у дітей з COVID-19.

Ключові слова: COVID-19, дисфункція щитоподібної залози у дітей, маркери запалення.

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