Recovery of patients from pediatric inflammatory multisystem syndrome (PIMS) and the impact of this disease on exercise tolerance

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Abstract

Background: Pediatric inflammatory multisystem syndrome (PIMS) is a rare but serious condition that typically manifests in children as a complication 2-4 weeks after they have been infected with the coronavirus disease 2019 (COVID-19). It is characterized by a wide range of symptoms, including high fever, inflammation of multiple organs, and potentially life-threatening complications. Early recognition and prompt medical intervention are crucial in managing PIMS and minimizing its impact on children's health.

Aims: This study aimed to evaluate the performance of patients six months after undergoing PIMS and the impact of the disease on physical activity and functioning.

Material and methods: 52 children aged 0-17 years were included in the study. They were divided into two groups: study (B) and control (K). 13 patients in group B and 16 in group K took part in a fitness test with the 6-minute walk test (6MWT). Total of 30 patients were surveyed in the PIMS questionnaire. Medical records of 36 people with PIMS syndrome were also included.

Results: Patients from both groups in the 6MWT achieved results that were not abnormal, and no differences between them were observed. In the physical activity undertaken before and after PIMS syndrome, no differences were observed. The patients' health status improved six months after the disease. PIMS syndrome affected the deterioration of general health, increased fatigue, and the occurrence of headaches and sleep disorders but did not affect the desire for social interaction.

Conclusions: Exercise tolerance in children after PIMS syndrome does not differ from the norm. Having PIMS syndrome does not affect the physical activity undertaken by children. The patients' health status improved 6 months after hospitalization. Survival of PIMS syndrome affected fatigue, headaches, and sleep disorders but did not affect the desire to interact with peers.

Key words

pediatric inflammatory multisystem syndrome (PIMS), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), 6-minute walk test (6MWT), physical activity.

Introduction

Pediatric Inflammatory Multisystem Syndrome (PIMS) typically affects pediatric patients with an average age of 8 years, occurring more frequently in boys and among ethnic minorities [1]. It is recognized as a complication of coronavirus disease 2019 (COVID-19) or contact with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The onset of this syndrome is associated with dysregulation of the immune system, which occurs approximately 2-4 weeks after exposure to COVID-19 or contact with SARS-CoV-2 [2,3]. The disease often follows a severe and dynamic course, frequently necessitating hospitalization. While studies have not definitively identified other underlying medical conditions that predispose individuals to PIMS syndrome [1,4], rare comorbidities observed during its onset may include respiratory conditions like asthma (4.1%) and chronic lung disease (1.5%), as well as cardiovascular disease (1.3%) and immunodeficiency (1.0%) [1].

The diagnosis of PIMS is based on addressing six criteria, such as pediatric age (0-18 years), persistent fever for at least three days, high rates of inflammation, multi-organ damage - symptoms from at least two organs or systems (gastrointestinal, circulatory, nervous, respiratory, mucocutaneous and renal). Other causes of acute inflammation should be ruled out and associated with infection or exposure to COVID-19 over a period of 4-8 weeks, the last criterion of which is not mandatory [2]. The most common symptoms in PIMS syndrome are fever (99.4% of patients), gastrointestinal symptoms (85.6%), cardiovascular problems (79.3%), and shock (56.3%) [1]. Most patients require intensive care (73.4%) in the treatment process, including 3.8% continuous extracorporeal membrane oxygenation (ECMO). Despite the need for intensive therapy, the mortality rate of PIMS syndrome is relatively low, at less than 0.1%, and short-term outcomes are favorable [1].

Multisystem inflammatory syndrome can develop cardiac complications such as acute myocarditis with decreased left ventricular ejection function (LVEF), hypotension, pericardial fluid, cardiac arrhythmias, and coronary artery aneurysms. The latter are among the most common permanent complications and can occur regardless of the phenotype and severity of the disease. This indicates the need for access to cardiology consultation and facilities in the form of a pediatric intensive care unit (ICU) [2].

Aims

Evaluation of patients' performance following six months of PIMS syndrome, the impact of the disease on the physical activity undertaken, and functioning six months after the disease.

Material and methods

Study participants

All subjects were informed about the study and gave written consent to participate. The study was carried out at two medical institutions: the Professor Jan Bogdanowicz Children's Hospital in Warsaw (Poland) and the Children's Memorial Health Institute in Wasrsaw (Poland) (in Polish: Instytut "Pomnik – Centrum Zdrowia Dziecka"). The study in the control group was carried out in the kindergarten "Piccolo Leonardo" in Warsaw (Poland) and in the Primary School No. 3, named after the Liaison Officers of the Home Army in Józefów (Poland).

Study groups

The study involved a group of 52 children aged 0-17 years and divided them into a study group and a control group. Study group (S) – children with PIMS syndrome (36 subjects: 18 girls and 18 boys) aged 0-17 years. Control group (C) – healthy children (16 subjects: 8 girls and 8 boys) aged 4-17 years.

Measurement tools

An original survey developed by the authors on PIMS syndrome – all patients who underwent PIMS syndrome between the ages of 3-17 years completed this survey. The survey was about the course of PIMS syndrome. The first part concerned the possibility of previous COVID-19 and the incidence of the disease in the child. It also checked the parents' subjective assessment of the child's condition at various intervals after leaving the hospital. Specifically, the child's physical activity was taken into account. Questions also included a comparison of the child's health before and after contracting PIMS syndrome.

The 6-minute walk test (6MWT) – six months after undergoing PIMS syndrome, children who had no contraindications to the test, with an age range of 4-17 years were tested. The 6MWT was also conducted in a control group. This test assesses submaximal performance. The 6MWT performed in the study was modified for children. The length of the corridor was 20 meters. A timer, a blood pressure monitor, a pulse oximeter, and a notebook were used to record the results, as well as a phone in case a doctor needed to be called. Calculation of the norm for a given patient was done according to the below Richard Geiger equation for girls and boys [6].

$$\text{Females 6MWT} = 188.61 + (51.50 \cdot \text{Age}) - (1.86 \cdot \text{Age}^2) + (86.10 \cdot \text{Height})$$
$$R^2 = 0.50, \text{SEE} = 57.52$$

$$\text{Males 6MWT} = 196.72 + (39.81 \cdot \text{Age}) - (1.36 \cdot \text{Age}^2) + (132.28 \cdot \text{Height})$$
$$R^2 = 0.49, \text{SEE} = 66.72$$

Inclusion criteria for the 6MWT included: (a) six months since PIMS syndrome (not applicable to control group), (b) age 4-17 years, (c) willingness to take the test and written consent from guardian, (d) comfortable shoes and clothing, (e) no meal immediately before the test, (f) no intense exertion 2 hours before the test, (g) taking prescribed medications (not applicable to the control group), (h) use of orthopedic aids if using them (not applicable to the control group), (i) verbal order from a pediatric cardiologist and no contraindications to the 6MWT test [5,6].

Study course

Before taking the test, each child was consulted by a pediatric cardiologist, who determined that there were no contraindications to performing the 6MWT. Each subject was instructed on what the test consisted of, and their preparation for the test was checked. Before taking the test, the patient rested for at least 10 minutes so that proper measurements of blood pressure, heart rate, and saturation could be taken. While walking, if necessary, the test subject was allowed to stop and report symptoms such as headache and dizziness, shortness of breath, chest pain, nausea, and other disorders. Each interruption of the test was noted by the investigator. At the "start" signal, a 6-minute countdown was started, and the patient started from the starting line and walked the designated distance as fast as possible by walking but not running. Every minute, the patient was informed of the remaining time until the end of the test. After 6 minutes, the instruc-

tor signaled the end of the test and measured the patient's heart rate, blood pressure, and saturation, asked about fatigue on the Borg scale, and the distance the patient had walked. Based on the formula from the article, the predicted norm for the child was calculated and compared with the value obtained. The child's parent was informed of both results.

Statistical analysis

Statistical analysis was performed using STATISTICA software version 13. Statistical tests were selected based on the distribution of the variables, which was verified by the Shapiro-Wilk test. Parametric tests (Student's T test or ANOVA analysis of variance) or their non-parametric counterparts (Mann-Whitney U test or Kruskall-Walis test) were used to analyze quantitative variables presented by the group. Variables expressed at the ordinal or nominal level were analyzed using tests based on the chi-square distribution. In the case of 2x2 tables, continuity correction was applied, while when the conditions for using the chi-square test were not met, Fisher's exact test with expansion was used for tables larger than 2x2.

Results

6-minute walk test

The study group included 13 patients, 6 girls and 7 boys, and 16 patients were included in the control group: 8 girls and 8 boys. The characteristics of the patients are shown in **Table 1**.

No statistically significant differences were observed between the 6MWT results except for the saturation, which indicates, on average, worse blood oxygen saturation in the study group. There was no statistically significant distance difference or difference in distance and norms between the study and control groups (**Tables 2** and **3**).

Author survey

The survey was completed by 30 people, including 16 girls (54.3%) and 14 boys (46.7%). The average age of the respondents was 6.98 years ± 3.95.

It was found that 33% of respondents were ill with COVID-19 within 8 weeks. Contact with a person with COVID-19 that was confirmed by a test had 43% of patients before the onset of PIMS syndrome. As many as 67% of respondents said

Table 1. Characteristics of the study groups.

Characteristics	Study group (S)	Control group (C)
Number of subjects	13	16
Body height [m]	1.4 ± 0.2	1.3 ± 0.2
Body weight [kg]	36.0 ± 9.4	28.2 ± 13.8
BMI [kg/m^2]	17.7 ± 3.7	16.0 ± 1.9
BMI interpretation	Underweight 23% Normal 46% Overweight 31%	Underweight 6% Normal 88% Overweight 6%
Age [years]	9.4 ± 2.3	8.2 ± 2.4

Table 2. Summary of average results from the 6MWT of the study and control groups.

Variable	Group	SBP 1 [mmHg]	DBP 1 [mmHg]	HR1 [bpm]	SpO_2 1 [%]	SBP 2 [mmHg]	DBP 2 [mmHg]	HR 2 [bpm]	SpO_2 2 [%]	Borg Scale
Mean	S	114.0 ± 10.5		82.2 ± 10.1		130.1 ± 16.4		101.9 ± 16.8		
	C	109.6 ± 9.5		87.4 ± 9.9		121.7 ± 9.6		94.7 ± 12.3		
Median	S		69.0		97.0		78.0		98.0	4.0
	C		66.0		98.0		77.0		99.0	3.0
Minimum	S		55.0		91.0		62.0		94.0	2.0
	C		55.0		97.0		54.0		98.0	2.0
Maximum	S		81.0		99.0		121.0		98.0	6.0
	C		102.0		99.0		87.0		100.0	8.0
p (S t-test)	S	0.250		0.179		0.096		0.191		
p (M-W U)	C		0.524		0.041		0.524		<0.001	0.910

Abbreviations: *6MWT – 6-minute walk test; S – study group, C – control group, 1 – measurement taken before 6MWT, 2 – measurement taken after 6MWT, SBP – systolic blood pressure, DBP – diastolic blood pressure, HR – heart rate, SpO_2 – saturation, bpm – beats per minute, S t-test – Student's t-test; M-W U – Mann–Whitney U test.*

Table 3. Summary of average results from the 6MWT of the study and control groups.

Variable	Group	Distance [m]	Norm [m]	Distance diff. [m]	Distance diff. [%]	Age [years]	Height [m]	Weight [kg]	BMI
Mean	S	579.6 ± 86.1		-10.0 ± 85.9	-1.5 ± 14.7		1.4 ± 0.2		
	C	560.6 ± 80.4		-2.1 ± 76.1	0.1 ± 13.0		1.3 ± 0.2		
Median	S		601.1			9.0		33.0	17.1
	C		545.8			7.0		1.3	15.7
Minimum	S		494.3			5.0		18.0	13.0
	C		488.2			6.0		1.2	12.2
Maximum	S		631.6			13.0		60.0	25.5
	C		688.4			13.0		1.7	20.8
p (S t-test)	S	0.546		0.795	0.758		0.129		
p (M-W U)	C		0.083			0.057		0.076	0.335

Abbreviations: *6MWT – 6-minute walk test, S – study group, C – control group, Distance – the distance the patients walked during the 6MWT, Norm – the predicted distance the patients should walk during the 6MWT according to the formula. Distance diff. – the difference created between the norm and the distance during the 6MWT.*

their child had contact with a person possibly ill with COVID-19 because the disease was not confirmed by testing. Fifty-three percent of the children had some other sign of illness indicative of immunosuppression within eight weeks of PIMS syndrome. 20% of parents said their child was frequently ill.

The child's recovery from PIMS syndrome was assessed based on the parental responses to a survey. The percentage of those who were in "very good" condition increased with time. In contrast, the percentage of those who were rated "bad" decreased slightly. The patients' health status was found to improve statistically significantly within six months from hospital discharge (p = 0.00005) (**Table 4**).

A total of 30% of patients were found to have any kind of memory impairment, which their parents described as forgetting words, the names of objects, learning regressions, and difficulties in memorization, reading, and counting. The patients' condition before and after the onset of PIMS syndrome was tabulated. Sleep problems, the occurrence of headaches, fatigue, the children's willingness to maintain social contacts, and general full health were analyzed (**Table 5** and **Fig. 1**).

Table 4. Summary of children's health status correlations at different intervals since the PIMS syndrome.

Pair of variables	N	R	interpretation	t(N-2)	p
Health status after discharge & after 1 month	29	0.598	strong correlation	3.873	0.001
Health status after 1 month & after 3 months	28	0.460	average correlation	2.644	0.014
Health status after 3 months & after 6 months	22	0.342	weak correlation	1.628	0.119

Notes: *Spearman's rank order correlation; missing data paired removed. Marked correlation coefficients are significant with p <.005.*

Table 5. The result of the statistical significance relationship of the variables tested by Chi^2 test or Fisher's test (2x2).

Variables	p
Fatigue before vs. Fatigue after	0.03333
Contact before vs. Fatigue after	1.0000
Headaches before vs. Fatigue after	0.31034
Sleep disorders before vs. fatigue after	0.65987
Full health before vs. Fatigue after	0.01806

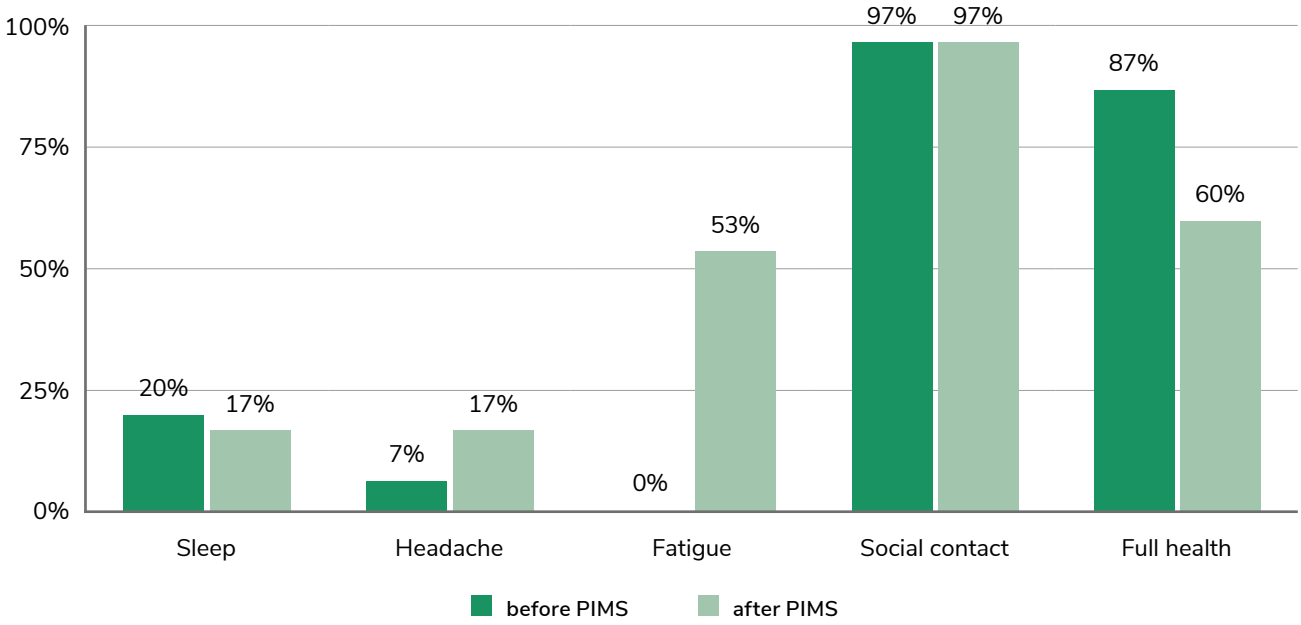

Figure 1. Percentage comparison of individual data before and after PIMS syndrome.

Medical records

During hospitalization for PIMS syndrome, the skin and mucous membranes were involved in 69% of children, the gastrointestinal tract in 72%, the respiratory tract in 56%, the nervous system in 64%, the cardiovascular system in 53%, and the urinary tract in 6% of children.

In the first of the skin and mucous membrane areas, there were symptoms such as fine/coarse rash all over the body and conjunctival injections/conjunctivitis, carmine lips, ocular erythema around the eyes, white coated tongue, erythematous lesions on the body, sore throat, hives, swelling, peeling skin.

In the area of the digestive system, the following were observed: abdominal pain, nausea, vomiting, diarrhea, ascites, constipation, loss of appetite, and gastrointestinal bleeding. Respiratory symptoms observed included: cough, runny nose, pneumonia (with pleural effusions), acute respiratory failure, pain and pressure during breathing, tachypnoe, dilated lymph nodes, and other respiratory infections. Neurological symptoms included headaches, weakness, e.g., irritability, fatigue, apathy, skin laxity, and positive meningeal symptoms, e.g., neck stiffness, spasticity, unconsciousness, and foot clonus. In the area of the circulatory system, the following were observed in children with PIMS syndrome: myocarditis, circulatory failure, mitral valve regurgitation, coronary artery involvement, repolarization abnormalities, tachycardia, decreased cardiac contractility, pericardial fluid, sinus bradycardia, palpitations (**Fig. 2**).

Discussion

As stated in the Introduction section, the average age of patients experiencing PIMS syndrome is 8 years, and 58.9% are boys [1]. In the 6MWT study group, the mean age was slightly higher at 9.4 years, and the percentage of boys (53.3%) slightly exceeded the percentage of girls who participated in the study. Hoste et al. [1], in their work, suggest an overrepresentation of the male gender. However, according to another publication, a clear gender predisposition to contracting multisystem inflammatory syndrome in children (MIS-C) has still not been established [7].

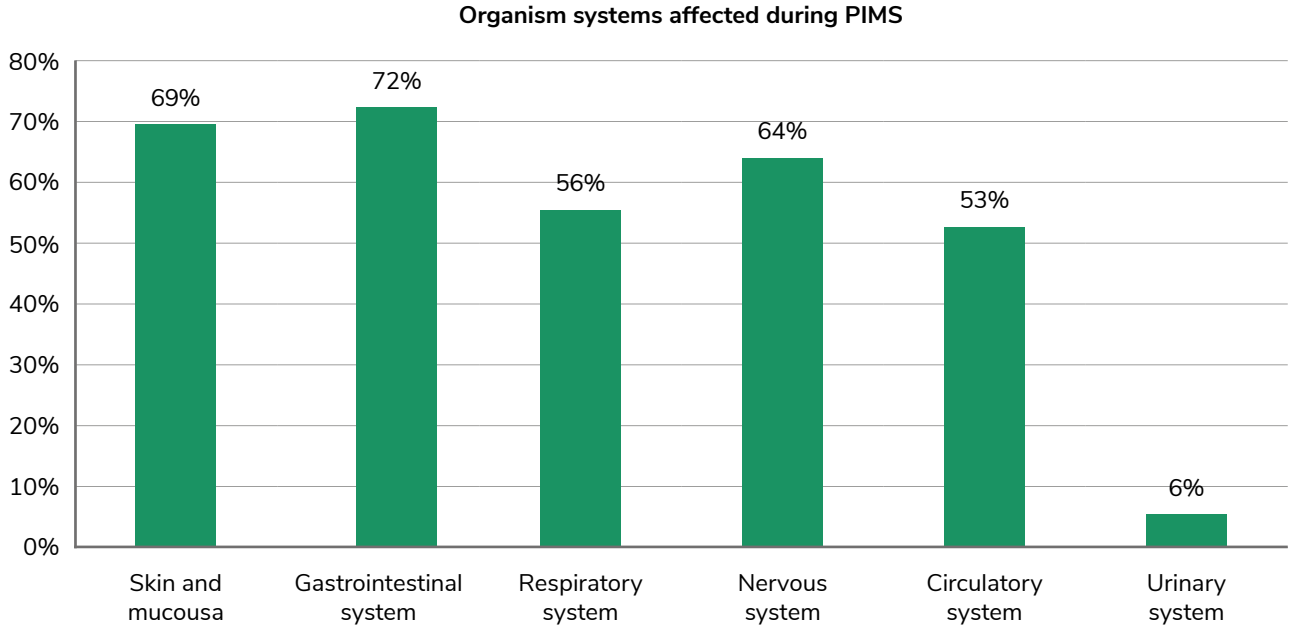

Figure 2. Percentage of affected particular systems in children with PIMS syndrome during hospitalization.

One article used the 6MWT as an indicator of a higher risk of death or heart transplantation in children with diastolic cardiomyopathy and chronic stable heart failure. A total of 49 children who performed the 6MWT were studied. The median age of the children was 11.9 years. The mean distance traveled by patients was 448 ±144 m, and the percentage of predicted value was 70 ± 21% [8]. In contrast, the mean distance walked in the present study was 579.6 ± 86.1 m, which is still a greater distance despite the lower median age. The percentage difference was exactly (-1.5 ± 14.7%) in the study group and (0.1 ± 13%) in the control group. The values did not show statistical significance.

One systematic review tested the distance of the 6MWT in children after undergoing severe illness. The subjects were evaluated at different time intervals. The results at 3 and 12 months after discharge from the hospital averaged 361 m and 436 m, respectively, which marked a significant improvement but still did not reach the norm [9]. Comparing the results of the present study: 579.6 m (± 86.1) in the study group and 589.6 m (± 80.5) in the control group, the patients in the studies by den Boer et al. [8] and Parry et al. [9] achieved significantly lower values.

It can be concluded that children show better cardiovascular adaptation than adults to prolonged efforts of moderate intensity. Avoidance of prolonged exertion by children has more of a psychological basis since the disruption of homeostasis is less than in adults.

This paper shows that children after PIMS syndrome achieve normal values in the 6MWT and consequently do not have a significant capacity impairment. The information gathered above on the adaptation of the respiratory and circulatory systems makes us think about the speed and ability of children's bodies to recover from a severe disease such as PIMS syndrome.

In addition, children at different periods - immediately after undergoing PIMS syndrome, six months after, and one year after the disease - showed a decreasing trend in the frequency of physical activity undertaken in respondents, but this decrease was not shown to be statistically

significant. Having PIMS syndrome did not significantly affect the physical activity undertaken by children.

All patients with PIMS syndrome from the present study were contraindicated to exercise for six months after the disease. Now that more and more is known about PIMS syndrome, only patients with myocardial involvement are contraindicated to exercise, and the restriction is temporary and is tailored individually to the patient depending on the presence of reduced cardiac contractility and whether the patient is taking cardiac support medications. It is very important to follow the recommendations of a pediatric cardiologist and abstain from physical activity in children, as this is to prevent possible complications, especially cardiac complications [2].

Theocharis et al. [10] described in detail the involvement of the myocardium during PIMS syndrome. Almost all of the patients examined had abnormal findings in cardiac and Doppler studies. More cardiac abnormalities were found to be present than originally reported. Particular attention should be paid to developing heart failure and coronary artery lesions. It was recorded that more than half of the patients had an ejection fraction of <55% on echocardiography (ECHO). Valvular regurgitation was present in as many as 75%, 60% of patients showed enlarged coronary arteries and pericardial fluid was present in 10% of patients. One patient had acute coronary syndrome due to subendocardial infarction.

Raffertya et al. [11] report that during PIMS syndrome, 72% of patients had a reduced LVEF by 30-50%, indicating mild to moderate cardiac dysfunction. Imaging studies described these abnormalities. In 71% of patients, there was complete recovery (LVEF > 60%). These patients achieved such a value for up to 7 days, with a median of 2 days.

The study by Hoste et al. [1] described that cardiovascular symptoms were found in 79.3%. Tachycardia was present in 76.6% of subjects, hypotension or cariogenic shock (59.9%). Myocarditis was observed in less than half of the patients (41.1%). Another cardiovascular abnormality observed was mild to moderate reduced left ventricular ejection fraction - LVEF 30%-55% (40.4%). In contrast, severe abnormalities (LVEF <30%) were rare (7.1%). Some patients developed coronary vasodilation (z-score 2-2.5; 11.6%) or aneurysms (z-score >2.5; 10.3%). Pericardial effusion was relatively common (22.3%). Occasionally, there are thrombotic complications (1.4%).

The medical records of the present study indicate that 53% of patients experienced cardiac complications. This is 19% less than in the article of Rafferya et al. [11] and 26.3% less than in Hoste et al. [1].

Dilatation of the coronary arteries is one of the complications. It poses a risk of clot formation, followed by myocardial infarction and sudden death. In the medical records of the present study, aneurysms accounted for 16% of cardiac disorders in children with MIS-C. Compared to the article by Hoste et al. [1], this does not represent a big difference, only about 6% more [1]. In contrast, it is a much lower percentage than the 60% in the cited paper by Theocharis et al. [10].

Another reason for limiting children's physical activity is myocarditis. Slightly more than half of the patients (58%) had myocarditis after PIMS syndrome. In the study by Hoste et al. [1], this disorder accounted for 41.1%, so 17% less. Most patients with myocarditis had a reduced: LVEF <60% had 48% of patients, LVEF< 55% had 37% of subjects, which is less than half, so it does not include as large a group as reported by Theocharis et al. [10].

Another observed cardiac complication after PIMS is hypotension associated with reduced ejection fraction (EF. In this case, there is a risk of developing dilated cardiomyopathy and acute heart failure. In the present study, 25% of children were diagnosed with hypotension. This is 34.9% less than in the study by Hoste et al. [1].

In 68% of patients, pericardial fluid was detected, which can cause impaired cardiac diastolic function. Compared to the study by Theocharis et al. [10], a significant difference can be seen, as only 10% of patients were observed to have pericardial fluid. In contrast, the Hoste et al. study [1] reported 22.3% of such patients. This difference may be due to the fact that in the present study, even a "trace of fluid" in the pericardium was marked as its presence.

The last cardiac complication that occurs after MIS-C is cardiac arrhythmias. They most often manifest as mild ventricular or supraventricular arrhythmias. Physical activity, in this case, may result in the perpetuation of these disorders. This disorder was present in 37% of the analyzed patients with cardiac complications.

On the other hand, at least six months after experiencing PIMS syndrome in the survey, 7.7% of people told us they were still experiencing cardiovascular complications. Respondents described this mainly as excessive fatigue. This complaint was experienced by as many as 53% of respondents in the first months after experiencing MIS-C, but it did not show statistical significance in the analysis.

LaRovere et al. [12] analyzed the incidence of neurological abnormalities with COVID-19 or MIS-C in patients younger than 21 years. Nervous system involvement was documented in 22%. Of these, 53% of patients with PIMS syndrome.

The study by Ray et al. [12] also presented neurological symptoms in patients with COVID-19 and PIMS syndrome. Of this group, 48% were patients with MIS-C and had the following neurological abnormalities ranked from most common to least common: encephalopathy (88%), peripheral nervous system involvement (40%), behavioral changes (36%), and hallucinations (24%). It was also noted that although there were more patients with COVID-19 than with MIS-C who had neurological symptoms, more patients with PIMS syndrome were admitted to the ICU (80%). In addition, 28% of those with PIMS-TS were discharged from the hospital with a disability, which was a slightly lower percentage than that of patients with COVID-19. Despite the rather detailed results, this study was conducted on an undersized group of 27 patients with COVID-19 and 25 patients with PIMS syndrome, so these data cannot be taken as a determinant but an encouragement for further research and not just short-term.

Comparing the above results with the data collected in this study from the medical records, 64% (n=23) of the patients collected had neurological symptoms during PIMS syndrome. The research cards recorded such symptoms as headache (n=12), weakness e.g., irritability, fatigue, apathy (n=10), skin hypersensitivity (n=5), positive meningeal symptoms e.g., neck stiffness (n=5), spasticity (n=1), unconsciousness (n=1), foot clonus (n=1).

On the other hand, at least six months after experiencing PIMS syndrome, 12.8% of respondents specified that their children had neurological symptoms. These early complications included memory lapses, difficulty remembering or recalling words, increased fatigue, and anxiety disorders. A separate question was devoted to memory lapses, and it was found that 30% of respondents had memory impairment (13.3% – minor; 10% – moderate; 6.7% – major). However, most of the respondents said that the memory disorders were gradually decreasing. Another complication was headache, which 10% of patients did not have before the disease.

No scientific studies were found with which to compare the complaints experienced after PIMS syndrome. Based on the survey, 56.4% of respondents experience complaints in their respective systems. It should be noted that 30% of patients experience memory disorders of varying degrees. Also, 53% of respondents struggle with increased fatigue. In contrast, 10% notice headaches that were not previously present.

Conclusions

Exercise tolerance in children six months after experiencing PIMS syndrome is normal. Survival of PIMS syndrome does not affect the physical activity undertaken by children. Children recover from experiencing PIMS syndrome. Survival of PIMS syndrome can cause more fatigue, headaches, and sleep disturbances. However, the ailments experienced after experiencing PIMS syndrome did not affect the willingness of social contact with peers.

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