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PIMS-TS- (Paediatric Inflammatory Multisystem Syndrome – Temporally Associated with SARS-CoV-2)- a new challenging medical condition

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Abstract:

At the beginning of pandemic of SARS-CoV-2 children were thought to go through COVID 19 in a definitely milder way than adults, in most cases even asymptomatically. However, even though the period of infection in pediatric patients is benign, SARS-CoV-2 found a way to take its toll on children's health. Here comes PIMS-TS: Paediatric inflammatory multisystem syndrome - temporally associated with SARS-CoV-2 (PIMS-TS) [ICD-10: U 10.9]. Since the global pandemic of COVID-19 is still on the go, for over a year now, SARS-CoV-2 tends to constantly mutate and affect children at increasingly young age either by oligosymptomatic respiratory viral infection, or more distant SARS-CoV-2-related medical condition- PIMS-TS.

Paediatric inflammatory multisystem syndrome - temporally associated with SARS-CoV-2 (PIMS-TS), or Multisystem inflammatory syndrome in children (MIS-C) as it's also called, is a rare systemic disease manifested by persistent fever and extreme inflammatory reaction following exposure to SARS-CoV-2, 2-4 weeks before the symptoms occur. It's a brand new medical condition, described for the first time in May 2020. PIMS-TS affects 1 out of 1000 children infected with SARS-CoV-2 and can lead to very dangerous cardiological

complications such as acute pancarditis, shock or aneurysms of coronary arteries. Efficient treatment performed in the accurate time and hospitalization in ICU allow to overcome PIMS-TS in the prevalent number of patients and get better in a few days. Mortality of PIMS-TS ranges from 1,5% to 2% of all cases.

Key words: COVID-19; SARS-CoV-2; PIMS-TS; INFECTIOUS DISEASES

Aim: The aim of this article is to summarize available knowledge concerning PIMS-TS and underline the importance of sharing experiences concerning this medical condition, which consequently becomes more and more common. The article sums up current recommendations including treatment methods, typical symptoms of PIMS-TS for individual systems of a human body, characteristic abnormalities in blood tests results, as well as possible changes detectable in imaging tests.

Materials and methods: PubMed & Google SCHOLAR databases and recommendations of Polish Paediatric Association were searched in July and August 2021. In PubMed & Google Scholar database we used medical publications involving terms „PIMS-TS". No language restrictions were added. Thirteen scientific articles published in the years 2020-2021 including recommendations of Polish Paediatric Association were scanned.

Conclusions: According to available data coming from Europe, China and the United States, children under 9 years old seem to present mild course of COVID-19 and lower susceptibility to SARS-CoV-2 infection. Nevertheless it's crucial to underline the possibility of occurring post-infection complication - PIMS-TS, which is very likely to become more and more frequent. Exchanging experiences concerning cases of PIMS patients among doctors all over the world is a key to successful dealing with this ascendingly common problem.

Introduction:

Paediatric Inflammatory Multisystem Syndrome – Temporally Associated with SARS-CoV-2 seems to form a brand new challenge for pediatricians, which can create a separate branch of the battle with widespread pandemic of COVID-19. The very first reports of PIMS come from United Kingdom and were noticed at the beginning of May 2020. It is known that PIMS symptoms are caused by multi system inflammatory reaction of the organism, potentially associated with immunological background. Course of this disease may bring to mind other pediatric inflammatory diseases such as Kawasaki disease, toxic shock syndrome or MAS-macrophage activation syndrome.(10) PIMS-TS is a disorder that includes numerous symptoms that come from almost all systems of the human body.

The most common symptoms are persistent fever, generalized inflammatory reaction and multi-organ dysfunction associated with exposure to SARS-CoV-2 virus, which usually occurs few

weeks before the onset of symptoms in the child. The time from exposure to the SARS-CoV-2 virus to onset of symptoms is still a matter of debate, however, it is estimated that symptoms appear in response to exposure to the virus 1 to 2 weeks earlier. Typically, in patients diagnosed with PIMS-TS syndrome, tests detecting the presence of the genetic material of the SARS-CoV-2 virus give a negative result, and the possible association of the clinical condition with this pathogen is established due to the presence of specific anti-SARS-CoV-2 antibodies.(8,9) Due to the nature of the symptoms, PIMS-TS syndrome is phenotypically overlapping with Kawasaki disease, which is an inflammatory disease of small and medium-sized vessels of unknown etiology. Its course is mainly characterized by inflammation of large coronary vessels, with subsequent formation of aneurysmal lesions and myocardial ischemia.(10) The symptomatic convergence of PIMS-TS and Kawasaki disease relies on the fact that the cardiological symptoms present in Kawasaki disease are one of the most dangerous and most common symptoms of PIMS-TS syndrome. As far as the cardiological symptoms are concerned, conducted studies showed that all children diagnosed with PIMS-TS show raised inflammatory/cardiac markers (CRP, ferritin, Troponin I, CK and pro-BNP). Transient valve regurgitation is present in 67% of patients. Left Ventricular ejection fraction is reduced in 80% of all cases. 93% of examined patients show coronary artery abnormalities. ECG abnormalities were present in 60%.(5,13)

The incidence of PIMS-TS syndrome is directly determined by the local severity of the SARS-CoV-2 virus epidemic, which is why there is a tendency for patients with this diagnosis to appear 3 to 6 weeks after the peak of the COVID-19 epidemic in the local population. (4)

Disease manifestations and diagnostic criteria:

In PIMS-TS, the clinical picture consists of symptoms from many systems of the child's organism. This is due to the molecular basis of this disease, i.e. disturbed homeostasis due to immune dysregulation. According to WHO, there is a diagnostic scheme that facilitates sorting out the symptoms and making an accurate diagnosis. A patient diagnosed with PIMS has to be a child aged 0 to 19 years with a persistent fever of more than 38.5 degrees Celsius for at least 3 days. In addition, the diagnosis of PIMS-TS syndrome requires symptoms from two of the following five groups: dermatological symptoms such as rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral „strawberry tongue", hands or feet); neurological symptoms such as hypotension, shock, and meningeal signs; cardiological symptoms such as: features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP); evidence of coagulopathy based on PT, PTT and elevated d-Dimers; gastrointestinal problems: diarrhoea, vomiting, or abdominal pain, appendicitis symptoms. Additionally, elevated markers of inflammation must be included in the diagnostic criteria. PIMS-TS patients show high levels of acute phase proteins such as: ESR, C-reactive protein, or procalcitonin. Exclusion of other causes is also needed to diagnose PIMS-TS.(5)

When assessing a patient suspected of PIMS-TS syndrome, other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes should be excluded. The final diagnostic criterion is the link to COVID-19. It includes positive results of tests detecting the genetic material of the SARS-CoV-2 virus, positive results of antigen tests, or the patient's seropositivity in terms of anti-SARS-CoV-2 antibodies, both in the immunoglobulin G and immunoglobulin M class.(11) To sum up, according to the WHO criteria, in order to diagnose PIMS-TS, a patient must meet the criteria of age, value and

duration of fever, show symptoms from 2 out of the 5 groups mentioned above, the patient should be associated with a case of exposure to SARS-CoV-2 virus, moreover should have elevated levels of acute phase proteins, other causes of the diagnosed clinical picture should be excluded.

CLINICAL ASPECTS:

All of the children with suspected / diagnosed PIMS should undergo blood tests and a general urinalysis. Blood test should include: blood culture (collected twice); anti-SARS-CoV-2 antibodies; blood count; Arterial Blood Gases; coagulology: D-dimer, fibrinogen, aPTT, INR; acute phase proteins: CRP, procalcitonin, LDH, ferritin; ionogram : sodium, potassium; triglycerides; NT-proBNP, Troponin I; phosphokinase; amylase, lipase; creatinine, urea; ALT, AST, GGTP, bilirubin; glucose. (3) In order to diagnose PIMS-TS we should observe a characteristic constellation of abnormalities in laboratory tests results such as: high level of an acute phase proteins like CRP significantly exceeding 10 mg/dl, lymphopenia, not significant anemia, hyponatraemia, hypoalbuminemia. high level of myocardial damage markers BNP lub NT-proBNP, troponin I. (2,3)

Unlike COVID-19, in the case of PIMS-TS, symptoms from the digestive system are observed very often. In this case, ultrasound should be the best and first diagnostic choice. Abdominal ultrasound studies show: thickening of the walls of intestines, peritoneal fluid, radiographic signs of appendicitis, gallbladder wall thickening, and enlargement of the mesenteric lymph nodes.(2,12)

Abnormalities in the results of radiological examinations are also observed in the course of the PIMS-TS syndrome.(1) Computed tomography usually reveals numerous consolidated interstitial densities, intensified in the region of the hilium of both lungs and in posterior parts of the lungs. Characteristic radiological symptoms in the course of PIMS-TS as well as COVID-19 are „ground-glass opacity" areas on both sides, interstitial changes in the form of thickening of the interlobular septum. thickening of the walls of the main and segmental bronchi, perihilar consolidation, lymphadenopathy, crazy paving pattern. Another pathology is a presence of a fluid sheath in the pleural cavities. Due to cardiological affection, characteristic for PIMS-TS, heart silhouette may be enlarged and pericardial effusion may be present(1).

What's important conducted analyses point out that the rate of PICU admissions for PIMS-TS is at least 11-fold higher than for similar inflammatory conditions. Although immediate survival is high, the long-term outcomes of children with PIMS-TS are unknown. (6)

Treatment:

The first line treatment is based on intravenous administration of immunoglobulins (IVIG), (7,12) while the second line treatment includes glucocorticosteroids such as: methylprednisolone. The indications for the use of drugs from the group of glucocorticosteroids are: persistent fever after 24 hours from the end of the IVIG infusion, anaphylactic reaction after using IVIG, or no access to IVIG.(2) The third line treatment includes biological drugs like: infliximab (TNF-alpha inhibitor), anakinra (IL-1 receptor inhibitor) and tocilizumab (IL-6 receptor inhibitor).(2) Serious or aggravating general condition of a child, shock symptoms, age below 12 months and coronary arteries aneurysms in ECHO are indications for

simultaneous treatment with IVIG and methyloprednisolon.(7),(12). Antiviral treatment is not recommended, only in very few cases, when patient tests positive for SARS-CoV-2 and SatO2 is below 94 %, the use of remdesivir is worth considering. (2,12) High levels of acute phase proteins (including procalcitionin) in a course of PIMS reflect disregulation of immunological system and aren't an effect of bacterial infection. Antibiotic therapy in that case is ineffective. (2,12)

Conclusion:

Each case of patient diagnosed with PIMS should be reported to national register of children's inflammatory diseases during pandemic of COVID-19.The analysis of a large group of patients allows to create an exact clinical profile of this disease, exchange treatment experiences, observations and capture the long-term effects of PIMS-TS. Nowadays, each young patient with symptoms of Kawasaki-like, inflammatory disease, or even showing signs of acute appendicitis should be examined and considered as a potential PIMS-TS patient. PIMS-TS is going to become more and more common in the nearest future !

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