

Kawasaki Disease Outbreak in Children During COVID-19 Pandemic.

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Short Report

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Abstract

Background

In response to the recent information about the outbreak of Kawasaki disease (KD) in children connected to SARS-Cov-2 pandemic, we would like to present a group of six patients hospitalized from March to May 2020 with an inflammatory disease similar to KD.

Findings

There were four girls and two boys, aged from 15 months to 16 years. They all presented with fever lasting at least five days, irritability, bilateral nonexudative conjunctivitis, lymphadenopathy, mucus membrane changes, rash, edema.

Neither the patients nor the other members of the patients' households had a positive history of COVID-19 infection. None of the six children had a positive PCR result for SARS-CoV-2 or a positive results for antibodies to SARS-CoV-2.

All patients received empiric antibiotic therapy. Four patients were diagnosed with KD. Three children received standard treatment. One boy did not respond and received an additional 14-days course of methylprednisolone.

In two girls, the diagnosis of KD was not made. All patients survived

Conclusion

Finding a correlation with the Covid-19 pandemic is difficult regarding the situation in our country. According to ECDC, in May 2020 Poland was still before the peak of the epidemic. The intention of this article is to report that increased hospitalization of children with the inflammatory syndrome is also observed in countries with low levels of transmission of the SARS-Cov-2 virus. Our observation may broaden the knowledge of new inflammatory syndrome, which is not necessarily caused by SARS-Cov-2 but may be worsened by co-infection.

Introduction

The etiology of Kawasaki Disease (KD) remains unclear. For many years infectious background was suspected. Many viruses (e.g. seasonal coronavirus – HCoV NL63, Epstein–Barr virus), bacteria, fungi were suspected – but nothing was proved (1). There is no doubt that genetic factors are important, but they cannot explain seasonal variations and temporal clustering of KD cases. In temperate regions, the peak of the incidence of KD occurs in the winter season. So far, there were several large epidemics of KD in Japan and in the United States (2). It has been hypothesized that tropospheric wind patterns arising from China are associated with KD peaks (3). It suggests that KD could be induced by an airborne pathogen from this area (3). Countries with large outbreaks of SARS-CoV-2 (France, Italy, Spain, UK, US) have seen the occurrence of cases of paediatric inflammatory, multisystem syndrome (PIMS) in the late stages of the first wave of the COVID-19 pandemic (4, 5, 6, 7, 8, 9). Lucio Verdoni and colleagues in the article "An outbreak of severe Kawasaki-like disease at the Italian epicenter of the SARS-CoV-2 epidemic: an observational cohort study" published in Lancet described a recent outbreak of KD in Italy (5). Clinicians in Europe and the United States have identified clusters of similar cases (3, 4, 5, 6, 7, 8, 9). Observed epidemic in KD disease in many countries is attributed to the Sars-Cov-2 pandemic.

Material And Methods

Between March 1st and May 31st 2020, at the Infectious Diseases Department in St. Joseph's Children's Hospital in Poznan (Poland), six children were hospitalized with an inflammatory disease similar to KD. We analysed only patients with fever without identified source and no response to antibiotic therapy. On admission, laboratory tests including complete blood count, C-reactive protein (CRP), potassium, sodium, and transaminase levels, urinalysis, blood and urine cultures, chest X-ray and abdominal ultrasound were performed. Children underwent cardiology consultation.

- KD was diagnosed in patients with fever lasting 5 days or longer accompanied by four or more of the clinical criteria: bilateral nonexudative conjunctivitis, erythema of the lips and oral mucosa, changes in the extremities, rash, and cervical lymphadenopathy (1).

PIMS-TS case definition criteria proposed by the Royal College of Paediatrics and Child Health, are described below (10):

A child is presenting with persistent fever, inflammation (neutrophilia, elevated CRP, and lymphopenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal, or neurological disorder) with other additional clinical, laboratory or imaging and electrocardiogram (ECG) features.

- Children fulfilling full or partial criteria for Kawasaki disease may be included.
- Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus.
- SARS-CoV-2 PCR testing positive or negative

Results

There were four girls and two boys, aged from 15 months to 16 years. They all presented with fever lasting at least seven days – not responding to antibiotic treatment, irritability, bilateral nonexudative conjunctivitis, cervical lymphadenopathy, mucus membrane changes: dry, cracked lips, pharyngitis, strawberry tongue, rash, peripheral edema. Inflammatory markers were elevated: neutrophilia with lymphopenia, significantly increased C-reactive protein, ferritin levels, and hypoalbuminemia. In some patients, raised troponin levels and transaminitis were also observed. Echo and ECG were performed in all patients – in one coronary artery dilatation was found.

Two patients were diagnosed with pneumonia. Abdominal ultrasound revealed lymphadenopathy, ascites, hepatosplenomegaly. Details are presented in the table 1.

There was no COVID-19 history, or COVID-19-compatible symptoms could be either elicited in the history of the child or a household member. None of the three tested children were positive for SARS-CoV-2 by PCR. All patients underwent serology tests: none was positive for IgG or IgA antibodies.

Coinfection with other pathogens has been investigated, and no pathogens have been detected: blood cultures were negative, there were no serological markers of Epstein-Barr virus infection (EBV), PCR testing for respiratory syncytial virus (RSV), and influenza was negative.

All patients received empiric antibiotic therapy. All children fulfilled PIMS-TS case definition criteria proposed by the Royal College of Paediatrics and Child Health. Four patients were diagnosed with Kawasaki Disease. Three children received standard treatment according to the American Heart Association: intravenous immunoglobulin (IVIG) 2 g/kg given over 12 h and aspirin 50 mg/kg. One boy did not respond to IVIG and received an additional 14-days course of methylprednisolone (11).

In two girls, the diagnosis was not made. The first patient was a 6-years old girl; she was admitted on the seventh day of fever. While hospital staying, she remained afebrile, and over ten days, other symptoms gradually resolved; cardiac echo was normal after two and six weeks from the beginning of a fever. The oldest girl had markedly increased inflammatory markers (CRP, ferritin), high NT-Pro-BNP (N-terminal pro-B-type natriuretic peptide), radiographic signs of pneumonia, but no changes were detected on echo. Fever subsided, and her condition improved without IVIG.

All patients survived, and their health status improved gradually with time.

Discussion

About 230 suspected cases of the inflammatory multisystem syndrome associated with SARS-CoV-2 infection (PIMS-TS) have been reported in EU/EEA countries and the UK in 2020 (4). The described increase in KD is similar to the situation observed in other countries (5, 6, 7, 8, 9). In past years we had a few patients with KD. In 2019 we had seven patients and in 2018 six (all cases in autumn/winter season). Finding a correlation with the Covid-19 pandemic is difficult regarding the situation in our country. Poland is a country with low transmission of SARS-CoV-2. As of 31st May we had over 20 000 cases (53cases /100,000); in our region (Wielkopolska), we had around 2000 cases (58.8cases/100,000)- mostly localized in provinces in the southern part of Wielkopolska. In those provinces, Covid-19 cases were mainly detected in long-term healthcare facilities for the elderly.

Since March 13, people were advised to self-isolate, schools, and kindergartens are closed. As pediatricians, we observe markedly decrease in infections in children. The number of children consulted in an emergency room and hospitalized is much lower comparing

to previous months. In other countries, PIMS is reported relatively late during the waning tail of the first epidemic curve – so this is not the moment for Poland. According to ECDC, in May 2020 Poland was still before the peak of the epidemic .

One possible mechanism that causes PIMS in children could be via antibody-dependent enhancement (ADE) (4, 7). All the examined patients were serologically negative when tested for the presence of IgA or IgG antibodies against SARS-CoV-2. The negative results can't be explained by the low quality of test. Both molecular and serological tests were performed in nationally certified laboratories. Negative tests results can be explained by the clinical context. Patients had no proven contacts with people with Covid-19, family members were healthy. So in the described patients, the inflammatory condition was not related to SARS-CoV-2 infection.

The intention of this article is to give information that an increase in hospitalization of children with an inflammatory syndrome is also observed in countries with low transmission of the SARS-CoV-2 virus. Our observation can broaden the knowledge on a new inflammatory syndrome, which is not necessarily caused by SARS-CoV-2, but it can be worsened by coinfection.

List Of Abbreviations

ADE- antibody-dependent enhancement

ALT - Alanine aminotransferase

AST - Aspartate aminotransferase

CRP - C-reactive protein

EBV – Epstein Barr virus

ECG - electrocardiogram

IVIG - intravenous immunoglobulin

KD - Kawasaki Disease

NT-proBNP-N-terminal pro-B-type natriuretic peptide,

PCR – polymerase chain reaction

PIMS - paediatric inflammatory, multisystem syndrome

RCA – right coronary artery,

RSV - respiratory syncytial virus

Declarations

Ethics approval and consent to participate

This is an analysis of medical data, no personal data were analyzed, so there was no need for ethics committee approval.

Consent for publication

On behalf of the authors I give consent for publication.

Availability of data and materials

All the data are available upon request

Competing interests

All the authors declare no conflict of interests.

Funding

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Authors' contributions

EG substantial contributions to conception and design, and acquisition of data, and analysis and interpretation of data; participate in drafting the article, revising it critically for important intellectual content; and give final approval of the version to be submitted

JW had substantial contributions to conception,; participate in drafting the article, revising it critically for important intellectual content; and give final approval of the version to be submitted.

MF had substantial contributions to analysis and interpretation of data; participate in drafting the article, revising it critically for important intellectual content; and give final approval of the version to be submitted.

DJ-L had substantial contributions to conception, design and interpretation of data; participate in drafting the article, revising it critically for important intellectual content; and give final approval of the version to be submitted.

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Table

Table 1.
Demographics, clinical findings, imaging findings, treatment, and outcome.

Age, gender, comorbidities	Clinical presentation	Laboratory results	Microbiology results	Imaging results	Pharmacological treatment	outcome
Patient 1 female 6 years Caucasian no comorbidities	7 days >39°C, conjunctivitis; rash, pharyngitis, strawberry tongue, lymphadenopathy, vomiting	CRP 85.9 mg/L; PCT 0.07ng/ml; ALT 12U/l;AST 14U/l;albumin 345g/L; platelets 655×10 ⁹ /l; lympocytes 1.06×10 ⁹ /l; neutrophils 6.36×10 ⁹ /l; hemoglobin 11.9g/l	Blod culture sterile Influenza PCR negative SARS-CoV-2 IgA negative, SARS-CoV-2 IgG negative, EBV IgG negative EBV IgM negative	No abnormalities on chest x-ray and abdominal ultrasound	cefuroxime	Resolution of symptoms, no abnormalites on echo on 2 and 6 weeks
Patient 2 female 16 years Caucasian no comorbidities	7 days 39°C, mialgia, headache, conjunstitivitis, lymphadenopathy, pharyngitis, strawberry tounge, haemorrhagic rash, peripheral oedema, pruritus	CRP 336 mg/L; PCT 3.96ng/ml; NT-proBNP 492pg/ml; ALT 141U/l; AST 216U/l; albumin 34 g/L; Ferritin 6690µg/L; D-dimers 10 mg/L; troponin 16 ng/L; platelets 199×10 ⁹ /l; lympocytes 4.94x 10 ⁹ /l; neutrophils 10.0x10 ⁹ /l; hemoglobin 12.7g/l	Blod culture sterile Influenza PCR negative SARS-CoV-2 PCR negative, SARS-CoV-2 IgA negative, SARS-CoV-2 IgG negative, EBV IgG positive EBV IgM negative	Bilateral basal lung consolidations, pleural effusions	ceftriaxone, clindamycin	Resolution of symptoms, no abnormalites on echo on 2 weeks
Patient 3 male 2 years Caucasian no comorbidities	7 days >39°C, irritability, conjunstitivitis, lymphadenopathy, cracked lips, pharyngitis, strawberry tounge, rash, peripheral oedema, diarrhoea	CRP 56 mg/L; PCT0.22ng/ml; NT-proBNP 143pg/ml; ALT 43U/l; AST 28U/l; albumin 41 g/L; platelets 678 ×10 ⁹ /l;	Blod culture sterile Influenza PCR negative SARS-CoV-2 IgA negative, SARS-CoV-2 IgG negative, EBV IgG negative	No abnormalities on chest x-ray and abdominal ultrasound	cefuroxime, IVIG, Aspirin	Good response, no abnormalites on echo on 2 and 6 weeks

		lympocytes 4.94x 10 ⁹ /l; neutrophils 9.2x10 ⁹ /l; hemoglobin 10.4g/l	EBV IgM negative			
Patient 4 male 3 years Caucasian no comorbidities	5 days >39°C, conjunctivitis; haemorrhagic rash, lymphadenopathy, strawberry tounge, cracked lips, periperal oedema, diarrhoea	CRP 67.5 mg/L; PCT 1.19ng/ml; ALT 244U/l, AST 161U/l, albumin 28g/l; platelets 386x10 ⁹ /l; lympocytes 2.75x 10 ⁹ /l ; neutrophils 17.26x10 ⁹ /l; hemoglobin 10.4g/l	Blod culture sterile Influenza PCR negative SARS-CoV-2 IgA negative, SARS-CoV-2 IgG negative, EBV IgG negative EBV IgM negative	Bilateral pneumonia	ceftriaxone, IVIG, methylprednisolone, aspirin	No response to IVIG, good response after steroid treatment, no abnormailites on echo on 2 weeks
Patient 5 female 4.5 years Caucasian no comorbidities	10days >39°C, conjunctivitis; rash, lymphadenopathy, strawberry tounge, cracked lips, periperal oedema	CRP 166 mg/L; PCT 0.05ng/ml; ALT 17U/l; AST 34U/l; albumin 28g/l; platelets 610x10 ⁹ /l; lympocytes 5.09x 10 ⁹ /l; neutrophils 4.37x10 ⁹ /l; hemoglobin 8.8g/l	Blod culture sterile Influenza PCR negative SARS-CoV-2 IgA negative, SARS-CoV-2 IgG negative, EBV IgG negative EBV IgM negative	Hepatomegaly, ascites	cefuroxime, IVIG, aspirin	Good response
Patient 6 female 15 months Asian no comorbidities	7days >39°C, conjunctivitis; rash, lymphadenopathy, strawberry tounge	CRP 67 mg/L; PCT 0.89ng/ml; ALT 9U/l; AST 18U/l; albumin 33g/l, platelets 386x10 ⁹ /l; lympocytes 2.75x10 ⁹ /l; neutrophils 17.26x10 ⁹ /l; hemoglobin 10.4g/l	Blod culture sterile Influenza PCR negative SARS-CoV-2 IgA negative, SARS-CoV-2 IgG negative, EBV IgG negative EBV IgM negative	Ascites, pleural effusion, dilated RCA	cefuroxime, IVIG, aspirin	Good response

ALT - Alanine aminotransferase, AST - Aspartate aminotransferase, CRP-C-reactive protein, EBV – Epstein Barr virus, IVIG-human intravenous immunoglobulin,

NT-proBNP-N-terminal pro-B-type natriuretic peptide, PCR – polymerase chain reaction, PCT -procalcitonin, RCA – right coronary artery,