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Multisystem inflammatory syndrome in Romanian children - A multicentric national retrospective study: Are there any differences between our cohort and published data?

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Abstract

Multisystem Inflammatory Syndrome in Children (MIS-C) is a complication that occurs 4 to 6 weeks after an infection with SARS-CoV2. The aim of the study was to compare our data to the published literature and secondly to see if there are any prediction markers of the severity of the disease. We conducted a multicenter national retrospective study based on a cohort of 80 patients diagnosed with MIS-C from 3 centers in Romania. Patients were divided into 4 groups according to age: under 1 year, 1-5 years, 5-10 years and above 10 years. We compared demographic characteristics, clinical symptoms, lab results and treatment. Most common symptoms were fever (97.5%), pharyngeal hyperemia (76.2%) and rash (47.5%). We demonstrated the multisystem involvement of the disease based on clinical examination and lab results. High mean CRP values were found: 53.78 mg/dl in the first group, 52.24 mg/dl in the second, 88.24 mg/dl in the third and 112.79 mg/dl in the last one. Same pattern of increased values for increasing age groups were found for ferritin levels, both of them being correlated with more days of hospitalization. Nearly all patients received IV corticotherapy and antibiotics and only half of them received IV immunoglobulin. To the best of our knowledge this is the first multicenter study regarding MIS-C in our country regarding similarities and differences between our patients and published data. We highlighted the importance of knowing possible evolution of the disease in order to choose the best treatment plan.

Key words: Pediatric health; COVID19; MIS-C.

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Introduction

More than 290 million people have been infected with the novel coronavirus, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and more than 5.4 million deaths occurred. A total of 3,308,480 cases of Covid 19 were reported in Romania until December 2022 [1]. Children under the age of 9 represented 5% and under the age of 19 represented 7.5% according to the National Surveillance Data [2]. Since March 2020, when pandemic was declared, COVID-19 disease in children had mild or asymptomatic forms in nearly all cases. Most interesting feature of the disease was the particular complication that occurs 4 to 6 weeks after the infection with SARS-CoV2 [3]. This particular syndrome was named Pediatric Multisystem Inflammatory Syndrome temporally associated with COVID-19 (PIMS-TS) in Europe and Multisystem Inflammatory Syndrome in Children (MIS-C) in the USA. United Kingdom NHS was first to notice cases of a severe multisystem inflammatory syndrome in children previously affected by Covid 19. In USA, on April 7th 2020, the first 6 month old child with MIS-C was described. He was initially diagnosed with Kawasaki Disease (KD) [3]. There are several hypotheses regarding the pathophysiology of this syndrome, most incriminating an autoimmune reaction of the body to the viral infection. MIS-C is considered to be either an exacerbated immune system response or a maladaptive response characterized by hyperinflammation and a cytokine storm. The link between COVID-19 disease and this syndrome was demonstrated by Yonker et al [4]. that found prolonged presence of SARS-CoV2 virus in the gastrointestinal tract of children suffering of MIS-C [5]. Kawasaki disease was one of the first diseases with which the syndrome was being confused. Shana Godfred-Cato and co. elaborate a score to distinguish MIS-C from KD. They attribute 1 point to abdominal pain, headache, pericardial effusion and CRP>10 mg/dl, 2 points to platelets <150x100/ uL, -1 point to rash and -2 points to mucocutaneous lesions. The likelihood of positive diagnosis of MIS-C increased as the score raises. Thrombocytosis is a characteristic of KD, while lymphopenia, increased d-dimer and ferritin value and cardiac findings like myocarditis with ventricular dysfunction are found more often in MIS-C [6].

Material and methods

We conducted a multicentric national based study comprising of a cohort of patients hospitalized between 1st of August, 2020 and 31st of December, 2022 in 3 centers in Romania: Clinical Hospital for Children Victor Gomoiu Bucharest, The National Institute of Infectious Diseases Prof. Dr. Matei Bals Bucharest and Emergency Clinical Hospital for Children Brasov. Bucharest, the capital of Romania, has a population of 2,142,300. Clinical Hospital for Children Victor Gomoiu is responsible for consultations and treatment for children in Bucharest and oversees around 30,000 emergency cases every year. The National Institute of Infectious Diseases Prof. Dr. Matei Bals has over 40.000 emergency presentation during an year and it is the referral institute for Romania. Brasov county is located in the central area of Romania and has a population of more than 300.000 inhabitants, according to the latest national survey. The Children's Clinical Hospital of Brasov is the largest pediatric hospital from this region (more than 200 beds) and serves as a tertiary hospital for 3 neighbor counties. The statistical results were obtain

using Microsoft Excel, from the Office 365 package and Matlab R2023b. The statistical analysis was performed with predefined tools, functions and package. The statistical correlation with a p value of less than 0.05 was considered. The Ethical Committee from each of the three hospitals has approved the study. There are 3 definitions for this disease formulated by the Royal College of Paediatrics and Child Health (RCPCH), World Health Organization (WHO) and Centers For Disease Control And Prevention (CDC). We included in our study 80 patients according to World Health Organisation case definition who met all 6 criteria of the following: 1. Children between 0 and 19 years; 2. Fever more than 3 days; 3. Clinical signs of multisystem involvement (at least 2 of the following): rash, bilateral nonpurulent conjunctivitis, mucocutaneous inflammation signs (oral, hands or feet), hypotension or shock, cardiac dysfunction, pericarditis, valvulitis, coronary abnormalities (including echocardiographic findings or elevated troponin/BNP), evidence of coagulopathy (prolonged PT or PTT, elevated D-dimer), acute gastrointestinal symptoms (diarrhea, vomiting or abdominal pain); 4. Elevated inflammation markers, including any of the following: ESR/CRP/procalcitonin; 5. Evidence of SARS-CoV2 infection - any of the following: Positive SARS-Cov2 RT-PCR/Positive serology/Positive antigen test/Contact with an individual with COVID-19; 6. No other obvious microbial cause of inflammation including bacterial sepsis and staphylococcal/streptococcal toxic shock syndrome [7].

Additional relevant information

We compared patients demographic characteristics (age, gender, comorbidities), symptoms of presentation (fever, hyperemic conjunctivitis, adenopathy, gastro-intestinal, respiratory, neurological, muco-cutaneous), lab results (PCR SARS-COV2, Ag. SARS-COV2, C-reactive protein, ESR, fibrinogen, ferritin, procalcitonin, Lactat Dehydrogenase (LDH), hemoglobin, white blood cells, lymphocytes, neutrophiles, platelete, D-dimeri, troponin, NT-proBNP, coagulation status, sodium, calcium, potassium, urea, creatinin, uric acid, aminotransferases, albumin, glucose, faringian and nasal swab, cultures), EKG, cardiac assessment and treatment.

Results

We divided the patients into 4 groups based on age: under 1 year with 6 patients, 1 to 5 years with 37 patients, 5 to 10 years with 26 patients and over 10 years with 11 patients. We found a mean age of 5.05 years. We analyzed the number of cases in each month of the years between 2020 and 2022 and we found more patients presenting at the emergency department in the period from September to February, with a peak in April also demonstrating the normal course of an infectious disease often described as multiple waves during the epidemic period characterized of an increase in case number.

Most common symptom is fever (78/80; 97,5%) followed by pharyngeal hyperemia (61/80; 76,2%). Symptoms similar to Kawasaki disease, such as rash (38/80; 47,5%) and hyperemic conjunctivitis (33/80; 41,2) also occurred. Gastrointestinal symptoms were as follow: loss of appetite (37/80; 46,25%), abdominal pain (24/80; 30%), vomiting (27/80; 33,75%), nausea (19/80; 23,75%) and stool abnormalities (22/80; 27,5%). The most common respiratory symptom was cough (35/80; 43,75%), followed

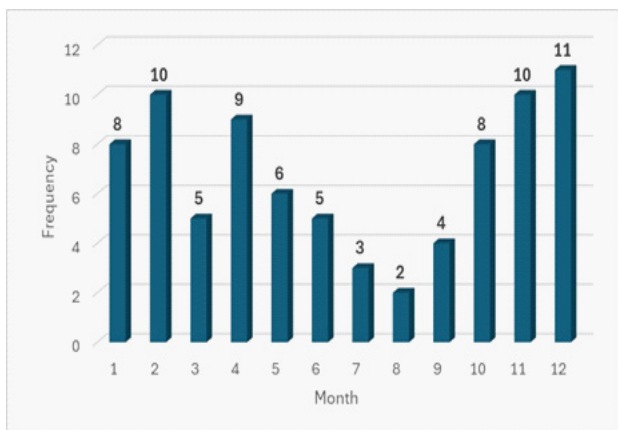


Figure 1: Distribution of cases according to the month of presentation to the emergency department.

Table 1: Symptoms found at presentations.

Characteristics	No.(%)
Mean age(years)	5.05
Males/Females	55/25(68,75%/31,25%)
Urban area/Rural area	46/34(57,5%/42,5%)
Known SARS-CoV2 infection	14(17,5%)
Fever	78(97,5%)
Pharyngeal hyperemia	61(76,2%)
Skin rash	38(47,5%)
Hyperemic conjunctivitis	33(41,2%)
Gastrointestinal manifestations	53(66,2%)
Abdominal pain	24(30%)
Vomiting	27(33,75%)
Nausea	19(23,75%)
Stool modifications	22(27,5%)
Respiratory manifestations	38(47,5%)
Cough	35(43,75%)
Pulmonary rales	12(15%)
Respiratory distress	9(11,25%)
Cardiovascular manifestations	18(22,5%)
Heart rate	18(22,5%)
Neurological symptoms	20(25%)
Headache	16(20%)
Signs of meningism	5(6,25%)
Altered mental status	2(2,5%)
Paresthesia	1(1,25%)
Myalgias	5(6,25%)

by pulmonary rales (12/80; 15%) and respiratory distress (9/80; 11,25%). Cardiovascular manifestation were found: changes in heart rate (bradycardia or tachycardia) (18/80; 22,5%). Some of the patients had neurological symptoms: headache (16/80; 20%), signs of meningism with neck stiffness (5/80; 6,25%), altered mental status (2/80; 2,5%) and paresthesia (1/80; 1,25%).

Inflammatory markers were found in all patients with higher median value in older children. In patients younger than 1 year median values were: 51,27 mg/dl for C-reactive protein (NV 0-1), 206,57 microg/l for ferritin (NV 10-120), 60,61 mm/1h for erythrocyte sedimentation rate and 317,51 U/l for Lactate Dehydrogenase (LDH) (NV 135-225). In contrast, in the group with patients over 10 years, the median values were significantly higher for C reactive protein (121,72 mg/dl), and ferritin

(849,63 microg/l) but lower for erythrocyte sedimentation rate (36,66 mm/1h).

We found a significant p-value for CRP between the group of patients with less than 1 year and the group of patients between 1 and 5 years ($p=0.04$), for ferritin between the group of patients between 1 and 5 years and the group of patients with greater than 10 years ($p<0.01$) and for D-dimer between the patients between 1 to 5 years and the group of patients with age greater than 10 years ($p<0.02$). We also demonstrated a statistical correlation between days of hospitalization and high levels of CRP ($p<0.005$) and ferritin ($p=0.003$). Complete blood count shows, out of 80 patients, higher values of leukocytes in 37 patients (NV 4500-13000/microL) with lower values of lymphocytes in 25 patients (NV 1500-6500/microL). Anemia was found in 42 patients (NV of Hemoglobin 11,7-16,6 g/dl). We also found high values of cardiac enzyme (troponin and NT proBNP) in the group with patients over 10 years old. Coagulation markers were high in all 4 groups such as D-dimer that were higher than normal range in 36 patients with a median value of 2,98 microg/l (NV<0,5) and fibrinogen with a median value of 505,97 mg/dl (VN 160-450 mg/dl). Beside inflammatory and coagulation markers there was also an electrolyte imbalance in a few patients: 1 patient with hypernatremia (NV 136-145 mmol/l), 6 patients with hyperkalemia (NV 3,5-5 mmol/l) and 4 patients with hyperchloremia (NV 90-106 mmol/l). Hepatic enzymes were also higher than normal in 16 patients out of 80 (20%) (VN ALT<40U/l; AST<37U/l).

Treatment in more than half of the patients was with immunoglobulin IV (48/80; 60%) and nearly all received corticotherapy (75/80; 93,75%). Also 77 patients out of 80 (96,25%) were treated with antibiotics. Other treatments such as anticoagulation therapy was administered in 32 patients (40%) of which only 19 patients (23,75%) had d-dimer values higher than normal. Other treatments that were administered were: at one patient antiviral therapy, 2 patients had received antiedematous therapy (mannitol), 4 patients albumin and other 2 patients antifungal therapy.

Discussion

To the best of our knowledge this is the first study for Romania regarding MIS-C comprising three different hospitals in our country. The mean age of 5.05 years was lower than in studies from United States that showed a median age of 7.3-10.8 years or studies from Italy with a mean age of 7.54 years. In our study we observed that more patients were in the group of 1 to 5 years (37 patients) followed by the group of 5 to 10 years (26 patients) [8,9]. Less patients were found in the other two groups: 6 patients with less than 1 year and 11 patients with more than 10 years. Studies made in Italy and the one made by Dufort in United States observed a higher incidence in children between 5 and 10 years [8,9]. We highlighted the high incidence of the disease in late fall and winter similar to the study from Italy that showed a higher incidence in December, February, March and April. Only 17 of our patients (17,5%) had a positive history of SARS-Cov2 infection, demonstrating the reduced severity of the disease in children and also providing an explanation why many of them were not tested [8]. Compared to published data, we found in our study similar results according to the symptoms, with 66.2% of cases presenting with gastrointestinal problems, 95% with mucocutaneous findings (pharyngeal hyperemia, conjunctivitis and rash) and 47.5% presenting with respiratory symptoms. The most frequently encountered symptoms in our study in children with MIS-C were fever, and pharyngeal

Table 2: Mean values of laboratory result.

Laboratory findings	Under 1 year	1-5 years	5-10 years	Above 10 years
CRP (mg/dl)	53.78	52.24	88.23	112.79
Ferritin (microg/l)	173.9	277.99	531.58	742.68
ESR (mm/1h)	69,33	51,56	45.64	38
Lactat dehydrogenase (U/l)	318.81	305,01	276,98	297,18
NT proBNP	2202.26	1867.3	1616.14	6512.49
D-dimer (mg/dl)	6.32	2.17	3.6	2.2
Fibrinogen	463,16	523.04	484.43	522.82
Natremia	136	136,2	136,7	137,18
AST	36,83	41.36	36.53	43.82
ALT	27,66	41.36	68.14	46.92

hyperemia with 97.5%, respectively 76.2% [10]. Neurological symptoms (headache, altered mental status, paresthesia and meningism) were found in 20 patients out of 80. Published articles pointed out that around 50% of cases presented with headache, which is more than what we found in our study. Also, in our study we did not find any patient with encephalopathy nor with seizures. Compared with published data where neurological involvement does not determine a severe outcome, our study describes a statistical correlation between neurological symptoms at presentation and number of hospitalization days [11]. ($p < 0.005$ for headache, $p = 0.02$ for altered metal status, $p = 0.03$ for paresthesia, $p = 0.02$ for signs of meningism) [12]. Lymphopenia is frequently found. It is demonstrated that its levels are correlated with severity and mortality of MIS-C. Interleukine-6, an inflammation marker, may trigger massive death of lymphocytes [13]. Lower levels of lymphocytes are a result of low levels of both CD4+ and CD8+ cells. In our study we found low levels of lymphocytes in 25 cases out of 80 (31,25%) and were correlated with prolonged hospitalization ($p = 0.01$). Our study highlights the differences in median value of the inflammatory markers between the 4 study groups with higher values in the older children, demonstrating a milder inflammatory response in younger children. Several published studies underlined that higher values of inflammatory markers are correlated with severity of the disease. We demonstrated no difference in CRP values between the first two groups of patients (less than 1 year and 1 to 5 year) and no difference between the second group (1 to 5 years) and the last group (more than 10 years) for Ferritin and D-dimer [14]. Overall high values of CRP and Ferritin may indicate a longer and more severe evolution of the disease in our children and they were correlated with more days of hospitalization. Differential diagnosis of MIS-C with other diseases such as macrophage activation syndrome toxic shock syndrome and Kawasaki disease is very difficult due to the fact that clinical findings are very similar. We found in our study a higher mean age of presentation compared to non- COVID-19 KD cases (median age 2.0-2.7y) [15,16]. Considering the unpredictable evolution of the disease and the limited data about the long-term sequelae, practitioners must follow several protocols and choose the beneficial strategy for each individual patient. Numerous guidelines have been developed to help in the management of the disease. All these guidelines recommend the use of Intravenous Immunoglobulins (IVIg) with a dose of 2 g/kg/dose as first line treatment. Because of the increased dose of IVIG that is require the patients are at risk of developing hemolytic anemia and volume overload [3]. In our study more than a half received immunoglobulin with no adverse effects. Corticosteroids are also frequently recommended especially in patients with shock or organ-threatening disease. In published literature we

find that corticosteroids were used after IVIg administration in those patients that did not respond to treatment. In our study 60% of the patients received both therapies from the beginning of the hospitalization and 25 patients received only corticosteroids without IVIg. After evaluating the coagulation factors, a small dose of aspirin may be used prophylactically, especially in patients who develop symptoms similar to Kawasaki disease. Some guidelines such as AAP or Children's Hospital and Clinics of Minnesota also add antibiotics to the treatment (vancomycin, ceftriaxone or clindamycin). Our study showed an increased use of antibiotics, although the etiology is considered to be a viral one, but we deescalate the antibiotic usage [3,7]. Guidelines recommend antibiotic discontinuation in patients with negative cultures and no signs of bacterial infection.

Limitations

Our study has several limitations. The number of enrolled patients was relatively small. We could not analyze the long term outcome of the patients due to the retrospective nature of the study and also because parents did not come back as requested for the follow up of their children. Finally, regarding treatment there was no reevaluation of antibiotic therapy, the patients receiving it in almost all cases.

Conclusion

To the best of our knowledge this is the first multicenter study regarding MIS-C in our country. We demonstrated the similarities and differences between our patients and published data and we highlighted the importance of knowing possible evolution of the disease in order to choose the best treatment plan. We also demonstrated the markers that can predict a longer and more severe evolution of the disease.

Declarations

Competing interests: None to declare.

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