CONSEQUENCES OF COVID-19 IN CHILDREN

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Abstract
Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is the first global pandemic of the 21-th century. At the beginning, COVID-19 infections were more common in adults then in children; however, in the following months, the number of pediatric infection cases increased significantly. As the pandemic evolved, it was soon evident that immune dysregulation inflicted by the virus, posed children at risk for their lives. This study aims to explore clinical and laboratory features of post SARS-CoV-2 infection in children hospitalized in the General pediatric Ward. Of the 87 children included in the study 48% of cases belonged to the age-group 0-2years old. The most common symptom was fever in 94% of cases. White blood cells were elevated in 56% of children. Increased inflammatory markers were C reactive protein, Fibrinogen, Ferritin, D-dimer, Platelets. Respiratory system was compromised in 86% of children. Children at any age may be infected with SARS-CoV-2. They suffer a less severe acute infection compared to adults, but the immune dysregulation that follows, pose them at risk of late inflammatory reactions that sometimes may be life-threatening.
Keywords: COVID-19, Children, Consequences, Immunity, Fever.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is the first global pandemic of the twenty-first century. It was first identified in December 2019 in Wuhan, China, where were reported a cluster of pneumonia cases arising from unknown causes. COVID-19 was initially reported to the World Health Organization (WHO) on December 31, 2019 [1]. On January 30, 2020, the WHO declared the COVID-19 outbreak a global health emergency. Soon COVID-19 spread worldwide and on March 11, 2020, the WHO declared COVID-19 a global pandemic [2]. On May 11, 2023, the COVID-19 public health emergency ended; however, COVID-19 continues to be a health risk. On April 5, 2023, WHO estimated confirmed COVID-19 infections numbered over 762 million individuals worldwide and have resulted in nearly 7 million deaths [3].

Childhood COVID-19 occurred early in the outbreak. The first pediatric case, which was reported on January 20, 2020 was a 10-years old boy from China. It was soon evident that children were less affected and suffer mild disease compared to adults [4, 5, 6]. SARS-CoV-2 is an enveloped, positive single-stranded RNA virus with a glycoprotein spike (S) on the surface. The virus enters into the cells by binding of the S protein to the cellular receptor ACE-2 (angiotensin-converting-enzyme-2) and priming of the S glycoprotein by the host cell serine protease TMPRSS2. ACE2 molecules are expressed on the cell membrane in the heart, intestine, kidney, endothelial and type 2 alveolar cells. SARS-CoV-2 limits the activity of the ACE2-mediated metabolic pathway and thus promotes the development of inflammation in the lungs and myocardium [7,8]. The milder morbidity in children, despite similar or higher viral loads compared to adults is partly explained by the differences in the pediatric immune system compared to adults [9]. Children develop a very effective protective mechanism against infection designated "trained immunity", which is created by mandatory vaccinations and frequent viral respiratory tract infections in early childhood. Early immune responses to viral infections in children are characterized by a higher activation rate of the interferon (INF)-related innate immunity response and by a higher level of Th1 and natural killer cells [10,11]. Further suggested explanations are alterations in T cell populations in adults due to continuous antigen stimulation and thymic involution, and the simultaneous presence of other viruses in the respiratory mucosa of children, competing with SARS-CoV-2 [12, 13]. Children also have fewer comorbidities and a stronger pulmonary regenerative potential than adults [14].

On April 24, 2020, the United Kingdom National Health Service issued an alert on an emerging pediatric inflammatory multisystem disorder. Since May 2020, several highly endemic countries reported an exceptional high incidence of multisystem inflammatory syndrome (MIS) in children. On 13 May, the Center for Disease Control issued a definition for a reportable case of MIS-C. An individual aged < 21 years with: a minimum 24-h history of subjective or objective fever ≥ 38.0 °C and severe illness necessitating hospitalization; two or more organ systems affected (i.e., cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, neurological); laboratory evidence of inflammation One or more of the following: an elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or IL-6; elevated neutrophils or reduced lymphocytes; low albumin; laboratory or epidemiologic evidence of SARS-CoV-2 infection Positive SARS-CoV-2 testing by RT-PCR, serology, or antigen or COVID-19 exposure within 4 weeks prior to onset of symptoms with no alternative diagnosis [15,16,17].

This study aims to explore clinical and laboratory features of post SARS-CoV-2 infection period in children.

METHOD & MATERIAL

This is a retrospective study. In it are enrolled 87 children, 0-14 years, hospitalized during January 2022- December 2022, in University Hospital Center "Mother Teresa", Tirana, Albania. All cases were Negative for Nasopharyngeal Reverse Transcription-polymerase Chain Reaction (RT-PCR) Test and Positive for Serological Test (IgM, IgG). Data were extracted from the clinical records. The parameters studied are: epidemiologic data, clinical features, laboratory parameters, treatment.

RESULTS

Of the 87 children included in the study Female was the gender most affected from the Multisystem Inflammatory Syndrome in Children (MISC) 57% and Males were less affected 43%. (Fig.1)

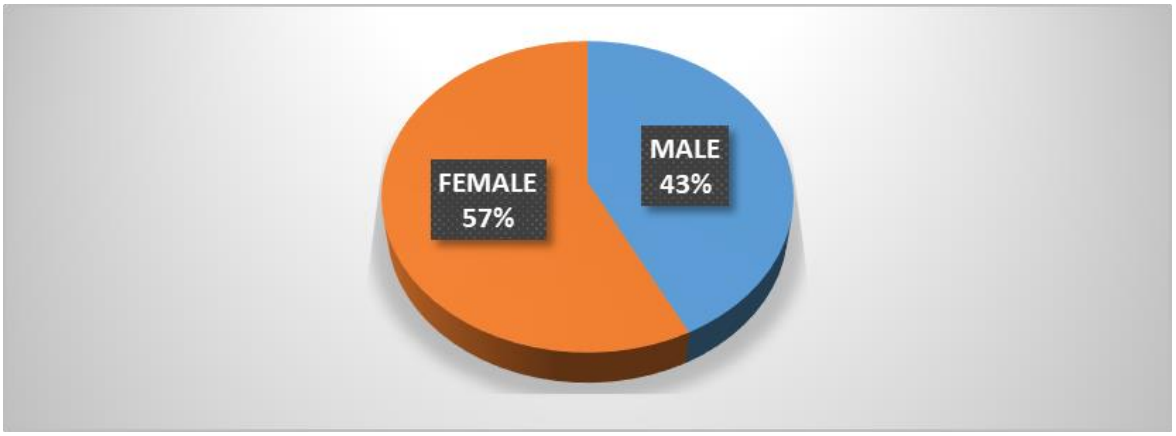

Figure 1. Gender Distribution of cases.

Most of the children belong to the age group 0-2 years (48%), followed by the age group 2-6 years (31%), and the age group 6-14 years 21%. 1-2 years old was the most affected age 23%, followed by 0-1 years 19%. (Fig.2)

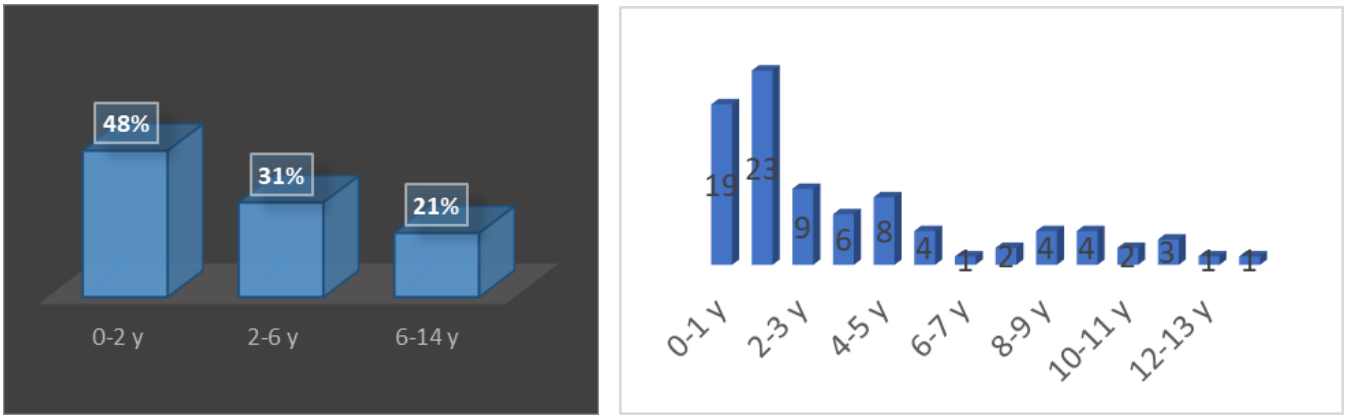

Figure 2. Age distribution of cases.

The clinical diagnosis on admission ranged from the most prevalent Fever without a Focus (53%), Fever of Unknown Origin (16%), Bronchopneumonia (10%), Gastroenteritis acute (8%), Abdomen acute (4%), Laryngotracheobronchitis (2%), Tonsillitis (2%), and Cervical lymphadenitis (1%). (Fig.3)

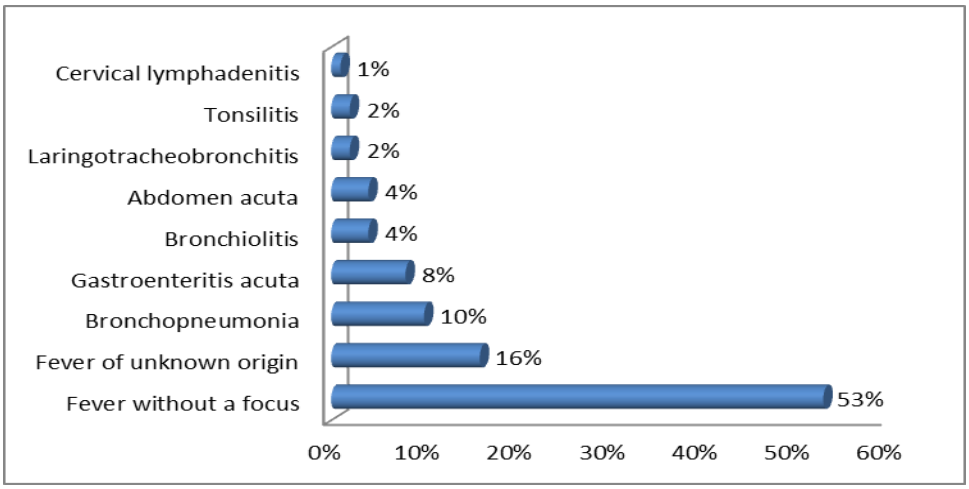

Figure 3. Clinical diagnosis on admission.

The most prevalent symptom was fever in 94% of cases followed by cough 47%, diarrhea 34%, fatigue 30%, vomitus 26%, anorexia 21%, abdominal pain 10% and joint pain in 5% of cases. (Fig. 4)

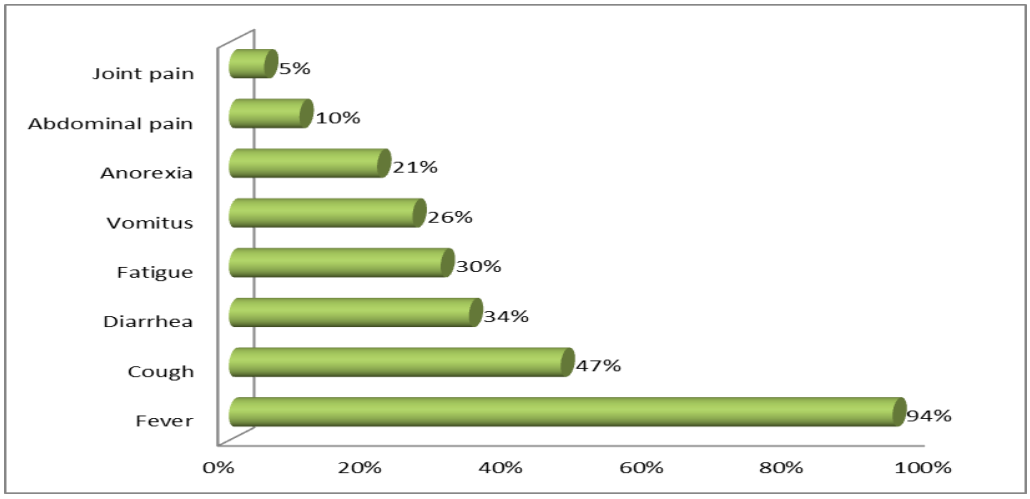

Figure 4. Symtoms

Elevated White blood cells >10,000cells/ml were found in 56% of cases. Elevated Platelets >400,000cells/ml were found in 58% of cases. High levels of C reactive protein were present in 66% of cases, high levels of Fibrinogen were present in 62% of cases, high levels of Ferritin were present in 37% of cases, and high levels of d-Dimer were present in 35% of cases.

Pulmonary changes were found in 86% of cases, most often as bronchitis 40%, followed by bronchopneumonia 35%, interstitial pneumonia 13% and lobar pneumonia 12%. (Fig.5)

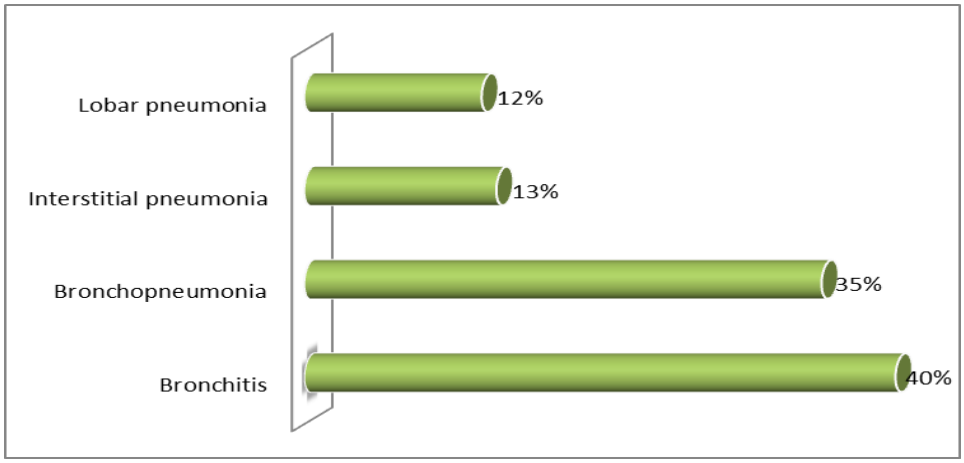

Figure 5. Pulmonary changes.

75% of children were treated only with broad spectrum antibiotics, in 21% was added corticosteroids, and in 4% of children was use intravenous immunoglobulin too.

DISCUSSION

Even though the burden of COVID-19 disease in children was not as heavy as in adults, children suffered too. In the first few months of the outbreak of the pandemic a novel syndrome emerged in children and adolescents. Known as Multisystem Inflammatory Syndrome (MIS), it had some common features with other inflammatory syndromes in children as Kawasaki Disease, Toxic Shock Syndrome [18,19,20]. The higher rate of positive of positive serologic tests compared to nasopharyngeal reverse transcription-polymerase chain reaction (RT-PCR), was suggestive of a late complication of the disease [21,22]. In the presented study all children were negative for the nasopharyngeal test, and positive for serological tests, most of them had IgG for SARS CoV-2 and a minority had both IgM and IgG for SARS CoV-2. Most of them denied having been in contact with persons with SARS CoV-2 infection, and none of them referred being ill in the previous months. All this information indicated that the children were asymptomatically infected with SARS CoV-2.

Pathophysiology of Multisystem Inflammatory Syndrome (MIS) is not entirely known, however possible mechanisms include; antibody or T-cell recognition of viral antigens expressed on infected cells, antibody or T-cell recognition of self-antigens (viral mimicry of the host) resulting in autoantibodies, formation of immune complexes which activate inflammation, viral super-antigen sequences which activate host immune cells [23,24]. Besides fever, the most common presentations of MIS are gastrointestinal, cardiovascular, muco-cutaneous, respiratory, headache, limb and periorbital edema. In children included in the study fever was the most consistent symptoms, followed by the respiratory tract involvement (cough), gastrointestinal tract (diarrhea, vomiting, abdominal pain), and at lesser extent constitutional symptoms (fatigue, anorexia, joint pain). The large genome of coronaviruses, seems to be the cause of the varied pathogenicity and ability to affect multiple organs. The vast diabase of the clinical diagnosis on

admission (from Fever without a focus to Cervical lymphadenitis), correlates with multiple organ affection in MIS-C [25,26].

Despite to the common features of MIS-C and Kawasaki Disease, there are several distinctions, and age is one of them. Patient with MIS-C were typically older than 7 years. However with the advancing of the pandemic the virus seemed to "have lost" his power, MIS-C was found in all age groups and was clinically less severe. In the presented study about half of the children (48%), were infants 0-2 years old, and the minority of them (21%) were older 6-14 years old.

Elevated inflammation markers are a mainstay feature of MIS-C. Cellular activation affecting multiple hematopoietic lineages is a constant feature too [27]. Of the laboratory findings indicating inflammation, white blood cells were increased in most of the children, although a minority of the presented with low white blood cells. Thrombocytosis was presented in most of the children (58%) and it is an additional sign of inflammation. Thrombocytosis in children are usually reactive, particularly common during recovery phase of an infection or inflammation and are usually transient and subsides when the primary stimulus ceases. Reactive thrombocytosis is usually mediated by increased release of numerous cytokines in response to infections. Despite the strikingly high platelet count, sometimes exceeding 1,000,000 cells/mm3, thrombotic and/or hemorrhagic complications are highly exceptional [28]. C reactive protein(CRP) was increased in most of the children (66%), it is an acute phase serum protein synthesized in the liver. Significant rise in CRP indicates clinically relevant inflammation. Fibrinogen which is an acute-phase reactant, produced by the liver, was increased too in most of the children (62%). Ferritin which is an acute-phase reactant that coordinates cellular defense against oxidative stress and inflammation was increased in 37% of children. D-dimer is the degradation product of crosslinked fibrin, it reflects ongoing activation of the hemostatic system, is increased in inflammation, trauma, malignancies. D-dimer was increased in 32% of the children with MIS.

Even though the children had multiple-organ involvement, increased inflammatory markers and needed hospitalization they were not severely ill and were not in need of intensive care. They were treated with broad spectrum antibiotics, 21% were in need of corticosteroids and in a minority of 4% were used intravenous immunoglobulins.

CONCLUSION

Children at any age may be infected with SARS-CoV-2. They suffer a less severe acute infection compared to adults, but the immune dysregulation that follows, pose them at risk of late inflammatory reactions that sometimes may be life-threatening. The exact incidence of these delayed hyper-immune response and the predisposing factors are not known. It is still hard to predict the mid and long term effects on children health and well-being.

COMPLIANCE WITH ETHICAL STANDARDS

Acknowledgments

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Disclosure of conflict of interest

Authors declare no conflict of interest.

Statement of ethical approval

The present research work does not contain any studies performed on animals/humans subjects by any of the authors.

Statement of informed consent

Informed Consent was taken from the parents of hospitalized children included in the study, for the interview and for using the data of their medical records, providing anonymity.

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