

CLINICAL AND EPIDEMIOLOGICAL CHARACTERISTICS IN CHILDREN CONFIRMED WITH SARS CoV-2 INFECTION IN A NON-COVID-19 PEDIATRIC CLINICAL HOSPITAL FROM ROMANIA IN THE FIRST 6 MONTHS OF THE PANDEMY

Spatariu Luminița*, Eugenia Buzoianu*, Sorina Chindriș*, Doina Anca Pleșca*

* University of Medicine and Pharmacy “Carol Davila”, “Dr. Victor Gomoiu” Children’s Clinical Hospital, Bucharest, Romania

ABSTRACT

The entire world has been facing the challenge of the new Pandemic with its epicenter in Wuhan, China, since December 2019. Current knowledge about SARS CoV-2 infection is still in its infancy and many questions have been awaiting an answer but what is apparently obvious, at least so far, is the low incidence of the disease among the pediatric population.

Thus, there is a need for sustained global and unitary efforts to define the clinical and immunological profile of the pediatric patient infected with SARS CoV-2. In order to present the experience of the Children’s Clinical Hospital “Dr. Victor Gomoiu”, Bucharest, Romania, which was declared support hospital for non-infectious pediatric pathology COVID-19, we have conducted an observational study that included 23 pediatric patients (0-18 years) confirmed with the new Coronavirus infection. The evaluation of the confirmed pediatric cases with SARS CoV-2 infection admitted in the hospital in the first 6 months after the declaration of the pandemy (11.03-09.09.2020), has been aiming to establish the epidemiological and clinical characteristics and to highlight the peculiarities of SARS CoV-2 infection in children in the study group. The results obtained from the study have shown a low incidence of the COVID-19 infection (1.2%) among the pediatric population but noticing the slightly upward trend starting with August 2020. There has been also a slight predominance of males, among confirmed positive patients (56.5%) and in terms of the most frequently affected age group, it has been observed a higher number of cases in patients aged under 5 years (86.9%). Analyzing the clinical data of patients included in the study group, it has been observed that, they generally have forms of disease with mild or medium severity. The most common symptom in patients infected with SARS CoV-2 is fever (73,9%), either as a single symptom (21.7%) or associated with other digestive, respiratory, cutaneous or neurological manifestations (52.1%). A peculiarity of the clinical evolution of the SARS CoV-2 infection in children, is represented by the presence of some digestive manifestations (abdominal pain, vomiting, diarrhea) in 39.1%; at the same time, from a paraclinical point of view, a clear difference compared to the cases of the SARS CoV-2 infection in adults, is the absence of biological inflammatory syndrome in a high

percentage of infection in children (above 50% of patients included in the study) and the presence of lymphopenia in only 20% of children evaluated. Further research is needed to clearly outline the clinical and immunological profile of the pediatric patients infected with the SARS CoV-2.

INTRODUCTION

Since December 2019, humanity is facing a new pandemic, SARS CoV-2 virus infection. Throughout the history, the mankind has gone through other pandemics with devastating effects such as plague, cholera, typhoid fever, tuberculosis, these being just some of the infectious diseases, which marked the history of medicine. The field of medical research and the progress of science are astonishing and undeniable, but nevertheless, the effects of the new coronavirus infection seem difficult to manage globally. The epicenter of the outbreak of SARS CoV-2 infection was in Wuhan, China, with the subsequent spread of the virus soon reaching the proportions of a pandemic. Since the beginning of this year and so far worldwide, 33.558.131 people have been confirmed with COVID-19 infection and 1.006.471 of them have died [1, 2]. In Romania, until September 27, a number of 121235 were confirmed as cases with coronavirus infection and 4,687 were reported as deaths [2].

Considering the international epidemiological situation as a result of the spread of the infection with the new coronavirus, as well as the declaration of the “Pandemic” by the WHO on March 11, 2020, on March 16, 2020 in Romania it was decided to establish a state of emergency imposing special measures, both in the health system and in the socio-economic plan.

From March 20, 2020 in the “Dr. Victor Gomoiu” Children’s Clinical Hospital were adopted a series of measures regarding the development of the medical activity in accordance with the national protocols for surveillance of acute respiratory syndrome with COVID-19.

Analyzing the international as well as the national epidemiological data, there is a reduced impact on the pediatric population compared to adults. Globally, the incidence of the new coronavirus infection among children has increased from less than 3% at the beginning of the year, to more than 7% today [1, 2]. However, the deaths in pediatric age are extremely low compared to what happens in adults.

The low incidence of the disease among the pediatric population is a topic of high interest for current and future research. There are still many unanswered questions, but it is certain that this is most likely the consequence of a combination of factors. The literature mentions so far three main hypotheses regarding the low incidence of the new coronavirus infection in the pediatric population [3, 4, 5].

It has been shown that angiotensin convertase 2 (ACE 2) receptors would be the gateway into human cells for some coronaviruses, including the SARS CoV-2 virus; also the low expression of these receptors in the respiratory tract of children, could be

the explanation for which they are less vulnerable to SARS CoV-2 virus [4, 5]. More recent studies, however, question this theory because the category of patients under the age of one year in which ACE 2 expression is lowest, is still an extremely vulnerable group for the new Coronavirus.

Another hypothesis that has attracted the attention of researchers is the endothelial damage that occurred before the infection, which facilitates the spread of the inflammatory process.

Because there is a low incidence of diseases recognized as causing endothelial destruction (cardiovascular disease, diabetes) in the pediatric population, it is estimated that the spread of the inflammatory process is limited in the conditions of unhealthy epithelium [5].

Driven by the many viruses that children overcome in the first years of life, as well as the administration of vaccines, the innate immune system of children apparently plays an important role in the protection against SARS CoV2. This hypothesis seems to be increasingly exploited and requires special attention in the future, especially that the researchers increasingly mention some possible correlations between influenza immunization and protection against coronavirus [5].

Thus, although apparently less affected by the SARS CoV2 virus compared to adults and generally having mild to moderate disease, the children are considered as “*hidden victims of the pandemic*”, rather than its face [6]. The lives of the children from all over the world have so far been influenced mainly by socio-economic effects. The financial insecurity of families, the suspension of social services, the limited access to healthcare (delaying or postponing vaccinations, poor monitoring of chronic diseases, etc.), the limiting access to education among children from economically disadvantaged backgrounds, are just some of the indirect aspects of the pandemic on the pediatric population [6]. However, it should not be overlooked that, with the evolution of the pandemic, the number of COVID-19 cases in pediatric age is increasing and also, some severe or atypical forms of the disease are more and more frequently mentioned among the pediatric population.

The evaluation of the pediatric cases confirmed with SARS CoV-2 infection in “Dr Victor Gomoiu” Children’s Clinical Hospital in the first 6 months after the declaration of the pandemic (11.03-09.09.2020) given that the hospital was declared a support hospital for pediatric pathology Non COVID. The evaluation of the cases aims to establish the clinical and epidemiological characteristics and to highlight the particularities of the SARS CoV-2 infection in the children from the studied group.

MATERIAL AND METHOD

We conducted an observational study that included pediatric patients (0-18 years) confirmed with infection with the new Coronavirus.

The study was conducted at the “Dr. Victor Gomoiu”, Children’s Clinical Hospital, Bucharest, Romania, declared a support hospital for non-infectious pediatric pathology non COVID-19.

The inclusion criteria were: age of patients (0-18 years), hospitalization in the Children’s Clinical Hospital “Dr. Victor Gomoiu”, signs and symptoms included in the case definition for infection with the new Coronavirus and RT-PCR test (real time reverse transcription polymerase chain reaction) positive for SARS CoV-2 infection, harvested from nasopharyngeal exudate.

The definition of a suspicious case according to the Order of the Romanian Ministry of Health has undergone changes since the beginning of the pandemic until now, correlated with the epidemiological evolution of the disease in our country and the increase in the number of cases secondary to the community transmission. Two aspects were taken into account, namely the epidemiological context and the clinical picture. The epidemiological context concerns the travel history, the contact with suspicious or confirmed persons, the membership in social clusters. Currently, the case definitions for the acute respiratory syndrome with the new coronavirus (COVID-19) established by the National Institute of Public Health (INSP) and transmitted through the National Center for Surveillance and Control of Communicable Diseases (CNSCBT) mention:

Suspicious case is considered:

- any person, regardless of age, who has a sudden onset of fever and a cough
- any person with sudden onset of any three or more of the following signs and symptoms: fever, cough, asthenia, headache, myalgia, sore throat, coryza, dyspnoea, anorexia/ nausea/vomiting, diarrhea, impaired mental status
- any person with pneumonia, bronchopneumonia +/- pleurisy
- any person with severe acute respiratory infection (SARI) (fever or history of fever and cough and shortness of breath (shortness of breath) and requiring overnight hospitalization)
- children up to 16 years of age who have gastrointestinal manifestations (vomiting, diarrhea) not associated with food.

Probable case is considered:

- the suspected case as defined above but who declares contact with a confirmed case or is epidemiologically related to an outbreak with at least one confirmed case
- the suspicious case associating lung image suggestive of COVID-19
- people with a recent onset of anosmia (loss of smell) or ageuzia (loss of taste) in the absence of an identified cause
- an adult who died without an explicable cause, with respiratory failure who preceded the death and who was in contact with a confirmed case or who had an epidemiological link with an outbreak with at least one confirmed case, a person with laboratory confirmation of infection with SARS-CoV-2, regardless of clinical signs and symptoms.

The analyzed period was March 31, 2020-August 31, 2020. The first patient confirmed positive with SARS-CoV-2 RT-PCR test was hospitalized on March 31, 2020.

According to the internal protocol, patients requiring hospitalization were subjected to epidemiological triage. After admission, patients were isolated in the buffer zones and nasopharyngeal exudate was collected for RT-PCR testing for SARS COV2.

The study included the analysis of several parameters extracted from the observation sheets, namely: demographic data, medical history, epidemiological context of exposure to SARS CoV-2 infection, presence of comorbidities, symptoms present at hospitalization, results of laboratory investigations, imaging results and treatment administered during hospitalization. We processed the information with the help of Microsoft Explorer.

RESULTS

Out of the total number of children hospitalized in the hospital during the mentioned period, a number of 23 children were confirmed positive for SARS CoV-2 virus infection, representing 1.2% of the total hospitalizations. For the analyzed period, it is observed that between 31.03-30.07, 13 patients from the studied group were confirmed positive (56.5%), the other 10 patients (43.5%) being diagnosed between 01.08-31.08. Analyzing the distribution of the cases according to the patient's sex, we found that out of the total of 23 patients included in the study, 13 were boys (56.5%) and 10 were girls (43.5%), observing a slight preponderance of male. Regarding the distribution of the cases by age groups, we found that 20 children were under 5 years old (86.9%). Out of these, about 40% were infants (age under 1 year). Another peculiarity regarding the distribution of patients by age groups, was represented by the category of infants under 3 months of age. Thus, in the studied group 6 of the patients (26.1%) were under 3 months old. In order to identify the notion of potentially infectious contact, the evaluation was difficult. Only 2 cases (8.6%) specified some contact with confirmed case, but in other 5 cases (21.7%) the anamnesis raises the suspicion of potential exposure to infection, without specifying a clearly known contact. In the other cases, no information was provided on the significant epidemiological context for SARS CoV-2 infection.

The environment of origin of the confirmed positive children, was another epidemiological analyzed element. It was observed that 14 patients (60.9%) came from urban areas, 10 of them (71,1%) residing in our city.

The case analysis did not show the presence of significant comorbidities, only one patient in the analyzed group (4.3%) being known to have Down syndrome associated with congenital malformative cardiac pathology (atrial septal defect).

Analyzing the reasons for hospitalization the patients included in the study, we considered the establishment of clinical features. These are shown in the figure 1. Thus,

following the triad considered classic in the case definition for SARS CoV-2 infection (fever, cough, shortness of breath), we did not identify patients who show this association of signs and symptoms. However, 4 (17.3%) patients presented for fever and cough. The fever (body temperature above 38 C) was detected in 17 patients (73.9%). 6 of the patients included in the study (26.1%) were afebrile at admission and remained afebrile throughout the hospitalization period. 3 of these (13%) were asymptomatic, being hospitalized for the evaluation of a pre-existing chronic pathology. The test was performed as an epidemiological screening measure, according to the internal protocol for surveillance of SARS CoV-2 infection, in force at the clinic at that time. Fever as a unique clinical sign was identified in 5 patients (21.7%) and in 12 patients (52.1%) fever was associated with other manifestations (digestive, respiratory, cutaneous, convulsive).

The digestive symptoms such as diarrhea, vomiting, loss of appetite, was a reason for hospitalization for 9 patients (39.1%); 7 of them (77.7%) had fever associated with digestive manifestations. Appetite disorder, or refusal to eat, was identified in some of the patients confirmed positive, regardless of age. Thus, in 9 patients (39.1%) the family mentioned as a reason for presenting to the hospital, a significant decrease in appetite, 5 of these patients correlating with fever and digestive manifestations and 2 of them with a symptomatology respiratory in a febrile context (22.2%).

Skin manifestations such as maculopapuloerythematous rash, some lesions with urticarial appearance and purple elements were detected in only one case of those analyzed.

Because during the analyzed period the hospital's internal protocol mentioned the obligation to transfer positive patients to Infectious Diseases Hospitals designated for the care of patients infected with SARS CoV-2, the clinical evolution of the patients included in the study group could not be followed. Thus, 3 children were transferred to the National Institute of Infectious Diseases and 18 patients to the Infectious Diseases Hospital "Victor Babeş". With the exception of two cases in which the family requested home quarantine, the rest of the patients were transferred to hospitals for infectious diseases to continue to provide the necessary medical care.

The analysis of the laboratory data has shown that for 3 (13%) patients from the studied group no other laboratory investigations were performed except for the RT PCR test for SARS CoV-2. Among the patients in whom venous blood was collected for laboratory investigations, we found the presence of leukopenia in 4 patients (20%). Lymphopenia was presented in 4 patients (20%) and neutropenia in 4 patients (20%). The evaluation of CRP allowed us to obtain the following results: normal values (<5mg / l) in 12 patients (60%), increased values of CRP (> 25mg / l) in 6 patients (30%), 2 patients (10%) with values of slightly increased CRP (5-25mg / l). The other biochemical investigations were normal, except for one patient (5%) who had hepatocytolysis syndrome.

Symptoms

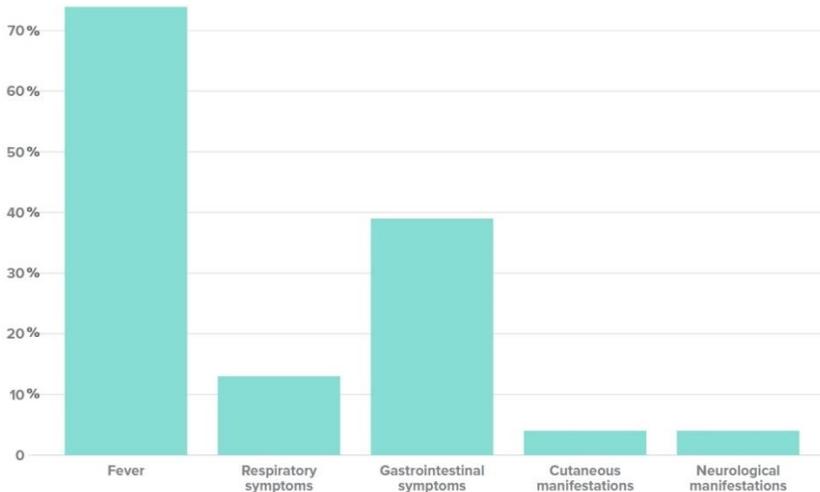


Fig. 1. Clinical features of the children with COVID-19 disease form “Dr. Victor Gomoiu” Children’s Clinical Hospital, Romania

DISCUSSIONS

The study performed on the group of 23 patients infected with the new coronavirus and evaluation the first 6 months of the pandemic in Romania in a Pediatric Hospital in Romania. The first case of COVID-19 infection in our country was confirmed on February 26, 2020 and the first case of an infected child from “Dr. Victor Gomoiu” Children’s Clinical Hospital was on March 31, 2020. Thus, compared to the beginning of the pandemic in our country, the incidence of SARS CoV-2 infection among pediatric patients admitted to our hospital was 1.2%, a figure similar to the data in the literature which mentions at that time, a low incidence of infection in children, namely: 1,2% China, 1,7% USA [2, 7, 8, 9, 10]. However, the data provided by the National Center for Surveillance and Control of Communicable Diseases during the analyzed period show that 3% of cases of SARS CoV2 were registered among children [2]. The low incidence of the infection among the pediatric population found also in our study, is influenced by several factors that have discussed several hypotheses [3, 4, 5]. It is important to mention that most children who have become infected are asymptomatic or develop mild/moderate forms of the disease, so underdiagnosis could be an explanation for the low incidence in this population group.

Following the dynamics of the evolution of the cases, it is observed that in the period 31.03-30.07.2020 there were confirmed positive a similar number of cases (13 cases), with those detected in the period 01.08.2020-31.08.2020 (10 cases).

The upward trend in the number of cases among children is correlated with data from the literature that draws attention to this phenomenon since August 2020, when schools were opened in many countries [1, 2, 6, 7].

The reopening of the educational institutions in some parts of the world, the relaxation of government measures and the increase in the number of people who have travelled for tourism could explain this significant increase in the number of new cases of SARS CoV2 infections, affecting both adults and the children. We have observed this phenomenon both in our country and worldwide.

The distribution of the patients in the study group by sex, has showed a slight predominance of males (56.5%) data, that are similar to those provided by the literature, but the small number of patients included in our study does not allow the formulation of significant conclusions.

The distribution by age groups has showed a higher number of cases in patients under 5 years of age as seen in table 1, a special category being infants (40% of patients in the group were under 1 year of age). Predominantly affecting infants it is correlated with data provided by several studies published in the literature. This result can be interpreted on the one hand in terms of age-related features (immature immune system, high receptivity to infections, etc.), the predisposition of infants to develop more severe forms of the disease (regardless of the etiological agent involved) and on the other hand by greater addressability to the tertiary medical service of families with children belonging to this age group.

Analyzing the clinical data of the patients included in the study group, it is observed that they generally present forms of disease with mild or medium severity, as it appears from the data provided by the literature. It should be noted that the clinical picture found in evaluated children in the study, is significantly different from that of adults [4, 8, 9, 10].

The clinical symptoms presented at admission by patients have drawn attention to possible features of SARS CoV-2 infection in children. Thus, it is observed that the clinical triad represented by fever, cough, shortness of breath has been found in a small number of cases in children compared to adults.

A peculiarity of the clinical evolution of the cases of SARS CoV2 infection in children, is represented by the presence of digestive manifestations (abdominal pain, vomiting, diarrhea). Digestive symptoms were reported in 39.1% of children included in the study group. These data are similar to those found in the literature [4, 11, 12]. The presence of digestive manifestations and especially the appearance of diarrheal stools is an important topic for future research, especially since the persistence of the SARS CoV2 virus in faeces has been demonstrated for a long time, raising questions about the mode of fecal-oral transmission. Another aspect that requires special attention in the future is the association between SARS CoV-2 infection and other especially viral infections. Underlying co-infections are more common in children

compared to adults [13, 14]. In the analyzed group, 2 (8.9%) of the patients confirmed with the infection with the new coronavirus, who presented digestive clinical manifestations, had concomitant infections associated with *Rotavirus*, *Adenovirus*, *Campylobacter*. These co-infections were confirmed by rapid tests.

A peculiarity regarding the distribution of patients by age groups correlated with clinical symptoms and paraclinical data was observed in infants under 3 months of age. The study group included 6 infants under 3 months of age, of which 2 patients (33.3% -both under 8 weeks of age) were hospitalized for fever, without other clinical manifestations, raising the suspicion of a systemic infections. The discrepancy between the clinical picture (persistent fever, general condition affected) and the laboratory data that refuted the suspicion of systemic infection (negative CRP, peripheral cultures and negative blood culture) attracted attention in these patients. Other 2 infants from the group of 6 patients under 3 months of age (33.3%) showed respiratory symptoms (cough, nasal obstruction, dyspnea) of moderate intensity.

Analyzing the paraclinical data of the patients included in the study group, it has been observed that the biological inflammatory syndrome was absent in over 50% of children. The data obtained being similar to those mentioned by other authors [4, 9, 11]. The literature mentions that adults infected with SARS CoV-2 and who develop severe forms of the disease are associated with lymphopenia and neutrophilia. These changes are part of the phenomenon described as the “cytokine cascade” [9, 11]. In the case of pediatric patients, the paraclinical changes are different from those that occur in adults, a finding highlighted in the analyzed group. Thus, lymphopenia was present in only 20% of the evaluated children.

Based on the models analyzed in the studies conducted in countries such as the United Kingdom, USA and Italy, there was a free interval of several weeks between the peak of confirmed positive cases in a given pediatric population and the first cases of multisystemic inflammatory syndrome in children [12]. The period analyzed by us represented the beginning of the pandemic in our country, which could explain the absence of severe cases of SARS CoV2 infection in the analyzed group but also the specifics of our hospital: we must point out that this hospital is not a hospital of infectious diseases, we cannot take care of children with SARS CoV2 infection. The small number of patients included in the study does not allow the formulation of additional conclusions. Further research is needed to more clearly outline the clinical and immunological profile of pediatric patients infected with SARS CoV2.

CONCLUSIONS

The SARS CoV-2 infection affects a small number of children compared to adults and most infected pediatric patients develop mild disease or are asymptomatic. A careful monitoring of pediatric infectious cases and in particular of infected infants and children with comorbidities is required. The association of SARS CoV-2 infection in

children and the onset of multisystemic inflammatory syndrome should also not be neglected. This association requires in-depth research in the coming period. Analyzing the epidemiological data obtained in this study reveals the need for sustained global and unitary efforts to define the clinical and immunological profile of the pediatric patient infected with SARS CoV-2.

In the future defining these profiles will help us to be capable of adopting the most effective measures to limit the spread of the viral infection, but also to establish the individualized unitary therapeutic options for the pediatric population.

Table 1. Comparison of clinical features and laboratory findings between pediatric patients, by age group

		Age 0 to ≤5 years (*n=20)	Age > 5 to ≤ 18 years (*n=3)
Epidemiological data			
Female patients		8 (34.8%)	2 (8.7 %)
Male patients		12 (52.2%)	1 (4.3 %)
Living environment	Urban area	12 (52.2 %)	2 (8.7 %)
	Rural area	8 (34.7 %)	1 (4.3 %)
Symptoms			
Fever (Body temperature > 38 °C)		5	-
Fever + Gastrointestinal symptoms		6	1
Fever + Respiratory symptoms		4	-
Fever + Cutaneous manifestations		1	-
Fever + Neurological manifestations		-	1
Laboratory tests (reference values)			
White blood cells (4.5 - 11.0 / 10 ³ /uL)		11	2
Decreased (*n)		3	1
Lymphocytes (1.10 - 4.80 / 10 ³ /uL)		14	2
Decreased (*n)		3	1
C-reactive protein (< 5mg/L)		10	2
Increased (5 - 25 mg/L)		1	1
Increased (> 25 mg/L)		6	-
* n= number of patients			

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