COVID-19 Pediatric Experience in a Portuguese Hospital: A Retrospective Clinical Analysis

A Experiência Pediátrica da COVID-19 num Hospital Português: Uma Análise Clínica Retrospetiva

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Abstract

Introduction: Since the World Health Organization announced the coronavirus disease-2019 (COVID-19) as a pandemic, its impact is seen every day. Despite the morbidity affecting the adult population, current evidence suggests that in children, COVID-19 causes milder symptoms.

Methods: This case series describes COVID-19 pediatric cases, diagnosed at the pediatric emergency department of Hospital de Cascais. A retrospective analysis was carried out, comprising the period from March to October 2020 describing clinical presentation, laboratory findings, treatment and outcome. Clinical data were obtained from the hospital records and the TRACE COVID platform, after informed consent from the caregivers.

Results: A total of 67 children out of 1974 tested (3%), were diagnosed with COVID-19 disease. The median age was six years-old, without gender predominance. Most patients presented with fever (76%) and respiratory symptoms (43%). Headache (30%) and myalgias (10%) were also frequently described. Gastrointestinal symptoms were reported in 43% of children, while only 6% experienced loss of taste or smell. Diagnostic confirmation was done with reverse transcription polymerase chain reaction (RT – PCR) from nasal and oropharyngeal secretions. Five children (7%) required laboratory testing, and the findings included leukocytosis and C-reactive protein (CRP) elevation. Three patients (4%) underwent chest radiography and none of them had abnormalities suggesting COVID-19 pneumonia. Disease severity ranged from mild to slightly moderate, with no complication requiring support treatment nor specific antiviral therapy. Among all patients, only one was transferred to a tertiary hospital; the others were discharged home. Follow-up was possible in 63 children (94%) and they became asymptomatic after a median of five days.

Conclusion: These results are similar to those found in international series and to the only Portuguese study published in 2020, from a tertiary hospital. This retrospective series supports current evidence, which states that children infected with SARS-CoV-2 have a milder clinical course than adults.

Keywords: Child; Coronavirus Infection; COVID-19; SARS-CoV-2

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Resumo

Introdução: Desde que a Organização Mundial de Saúde anunciou a doença pelo novo coronavírus (COVID-19) como pandemia, o seu impacto faz-se sentir diariamente. Comparando com os adultos, a evidência sugere que a COVID-19 nas crianças resulta em sintomas mais ligeiros.

Métodos: Descrição dos casos de COVID-19 diagnosticados no serviço de urgência pediátrica do Hospital de Cascais entre março e outubro de 2020, através da análise retrospetiva da clínica, achados laboratoriais, tratamento e evolução. Os dados foram obtidos dos registos hospitalares e da plataforma TRACE COVID, após consentimento informado dos cuidadores.

Resultados: Das 1974 crianças testadas, 67 (3%) foram diagnosticadas com COVID-19, com mediana de idade de seis anos, sem predomínio de género. A maioria das crianças apresentou febre (76%) e sintomas respiratórios (43%). Cefaleias (30%) e mialgias (10%) foram também frequentemente reportadas. Sintomas gastrointestinais foram descritos em 43% das crianças, enquanto 6% referiram anosmia ou ageusia.

A confirmação diagnóstica foi realizada através da pesquisa de SARS-CoV-2 por técnica *reverse transcriptase polymerase chain reaction* (RT-PCR) em amostras de exsudado orofaríngeo e nasofaríngeo. A avaliação laboratorial foi efetuada em cinco crianças (7%) e os achados incluíram leucocitose e elevação da proteína C reativa (PCR). Três crianças (4%) realizaram radiografia de tórax, todas sem alterações sugestivas de pneumonia associada à COVID-19.

A gravidade da doença variou de ligeira e moderada, sem complicações e sem necessidade de tratamento de suporte ou terapêutica antiviral específica.

Apenas um doente foi transferido para hospital terciário; os restantes tiveram alta para o domicílio. Foi possível aferir a evolução clínica em 63 crianças (94%), verificando-se uma mediana de cinco dias até resolução sintomática.

Conclusão: Os resultados desta série são semelhantes aos descritos em casuísticas internacionais e na única casuística nacional publicada em 2020 por um hospital terciário, sugerindo-se que, as crianças apresentem uma melhor evolução clínica que os adultos.

Palavras-chave: COVID-19; Criança; Infeção por Coronavírus; SARS-CoV-2

Introduction

In December 2019, a viral pneumonia with unknown etiology was reported in Wuhan, China. The causative agent was a novel coronavirus, later identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), closely related to coronaviruses responsible for previous severe acute respiratory syndrome (SARS) epidemics. As reported cases escalated in severity and rapidly extended to other countries, in March 2020, the World Health Organization (WHO) announced the disease caused by SARS-CoV-2 (COVID-19) as a pandemic.[1] Until this date COVID-19 has resulted in 93 million cases, and 2 million deaths.[2]

Since the Directorate-General of Health (DGH) provided guidelines for the management of suspect cases of COVID-19, specific procedures were adopted within our hospital from those. The first orientation was only applied to patients with fever and acute respiratory symptoms (cough, shortness of breath), without a clear etiology that fully explained the presentation, and a history of travel or residence, in an area reporting local SARS-CoV-2 transmission.[3] From there, due to the emergence of onward community transmission in Portugal, guidelines were further updated to include all patients with fever or acute respiratory illness.[4] A COVID-19 contingency plan was implemented at our Pediatric Department in March 24, 2020, that is still ongoing. It states that a RT-PCR SARS-CoV-2 swab of nasal or oropharyngeal secretions should be performed in all children and teenagers presenting with fever and acute respiratory symptoms (cough, dyspnea, odynophagia) and/or acute gastrointestinal symptoms (nausea/vomiting, abdominal pain, diarrhea), without other attributable cause, especially if there was a close contact with a confirmed or probable COVID-19 case (without a mask, for 15 minutes, indoors and less than two meters). Clinical records of suspect or confirmed cases are registered on a database, which is only available to the medical team.

According to our contingency plan, whenever a child is discharged home, follow-up is provided through telemedicine, to inform the test result, question about patient's well-being and provide orientation. After that the follow-up is provided by the family doctor through TRACE COVID platform. For discharge from home isolation, until the end of October, was necessary a negative COVID-19 test after being asymptomatic, but since then, it is only necessary symptoms resolution after 10 days.

If a child requires hospital admission and has a positive COVID-19 test, our contingency plan predicts patient's transfer to a tertiary pediatric care unit, until its full capacity is reached. If that happens, a specific pediatric ward in our hospital will be adapted to receive those COVID-19 patients.

This study aims to describe the clinical features, laboratory findings, treatment and outcome of children and adolescents, infected with SARS-CoV-2, diagnosed at the pediatric emergency department of Hospital de Cascais.

Material and Methods

We conducted a retrospective analysis, including all children admitted at our pediatric emergency department, with confirmed SARS-CoV-2 infection, between March (first diagnosed COVID-19 case) and October 2020 (a period of 195 days).

Collected data included demographic (gender, age group, risk factors, BCG vaccination, known contact with a positive case), clinical (fever, respiratory, gastrointestinal, neurological, cutaneous, sensorial or skeletal muscle symptoms), laboratory and imaging (chest radiograph or computed tomography-CT scan) records, as well as therapeutic options, clinical outcome and the need for hospitalization. Risk factors included: chronic respiratory or kidney disease, immunosuppression, heart disease, encephalopathy, neuromuscular disease, diabetes, metabolic disease, sickle cell disease and prematurity. The severity was defined according to the clinical manifestations referred in Table 1.

Clinical data was obtained from the hospital records and the TRACE COVID platform, after informed consent from the caregivers, and the statistical analysis was made with *Microsoft Excel*.

Obtained data was compared with that from international pediatric series and with the first published Portuguese pediatric case series, from a tertiary hospital – Hospital Santa Maria (HSM).

Results

Between March and October 2020, 67 out of 1974 (3%) children had a confirmed SARS-CoV-2 infection. Median age of infected children was six years old, ranging from one month and four days to 17 years-old, without gender predominance. Seven patients (10%) had at least one risk factor: prematurity, chronic respiratory diseases (asthma and recurrent wheezing) or cardiopathy (Table 2). Over half of the cases (58%) had a positive result from being in high-risk contact with another positive case, who was a co-inhabitant in nearly all cases. When investigated BCG vaccination, most children had received the BCG vaccine (79%).

All patients had at least one complaint, and the most frequent was fever (76%), followed by respiratory (58%), gastrointestinal (43%) and neurological (36%) symptoms. Over 50% of all febrile patients reported low grade fever, with a temperature under 38.5ºC. The most frequent respiratory symptoms were rhinorrhea and cough (43%), with four patients (6%) having shortness of breath, none with hypoxemia. Diarrhea (21%), abdominal pain (18%) and vomiting (12%) were the most frequent gastrointestinal symptoms. Most neurological manifestations were headaches, in 20 patients (30%), with one report of febrile seizure. Five children (7%) had non-specific skin manifestations like generalized macular and/or papular exanthems. Four patients (6%) mentioned anosmia and/or dysgeusia, all of them were over nine years-old (Table 3).

Almost all children (84%) had more than one symptom during the course of the disease, with fever and acute respiratory symptoms as the most frequent association, occurring in eight children (12%). In three different cases, patients described only one symptom: headache, abdominal pain and maculo-papular generalized rash.

Three patients (4%) had an initial SARS-CoV-2 negative test, performed between day one and three of the disease; as symptoms persisted, they were re-tested (two cases three days later and one case 19 days later), and had a positive result over the second time.

Five children (7%) required laboratory testing, and the findings included one case of leukocytosis (24.650/ mcL, 72% neutro-

Table 2. Demographic characteristics of SARS-CoV-2 positive patients.

	Total	≤ 3 months	4 - 11 months	1 year - 9 years	≥ 10 years
n (%)	67 (100%)	3 (5%)	11 (16%)	36 (54%)	17 (25%)
Risk factors	8 (12%)		1 Recurrent wheezing	1 Asthma	3 Asthma
			1 Prematurity	1 Prematurity	1 Cardiopathy

Table 1. Covid-19 disease clinical severity staging.

	Viral Stage (1-7 days)		Imune Stage (> 8 days)	
Severity	**Mild**	**Moderate**	**Severe**	**Critical**
Clinical features	Fever, odynophagia, headache, malaise, anosmia, conjunctivitis, cough, dyspnea absent	Dry cough, fever, myalgia, mild respiratory distress	Irritability, severe respiratory distress, hypoxia, tachycardia	ARDS, SIRS, shock, multiple organ dysfunction, coagulopathy, MAS/ HLH
Laboratory findings	Frequently normal – not indicated	Mild lymphopenia, Elevation of PT, ferritin, D-dimers and/or LDH	Elevation of D-dimers, LDH, ferritin, AST, CK, triglyceride NTpro-BNP, troponin, CRP and/or procalcitonin	Elevation of inflammation markers NT-pro-BNP, troponin, ALT, and creatinine Progressive cytopenia
Imaging findings		Chest X-ray with bilateral infiltrate	Chest X-ray and CT- scan with evidence of multiple lobar consolidation. Halo sign	

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ARDS: acute respiratory distress syndrome; CK: creatine kinase; CRP: C-reactive protein; CT: computed tomography; HL: hemophagocytic lymphohistiocytosis; LDH: lactate dehydrogenase; MAS: macrophagic activation syndrome; NT-ProBNP: N-terminal brain natriuretic peptide; PT: prothrombine time; SIRS: systemic inflammatory response syndrome.
Adapted from Sociedade Portuguesa de Infeciologia Pediátrica; Sociedade de Pneumologia Pediátrica e do Sono e Secção de Reumatologia Pediátrica (2020) - Abordagem do doente pediátrico com Covid-19 (p.7).

Table 3. Clinical manifestations of SARS-CoV-2 positive patients.

		Total (n = 67)
Fever		51 (76%)
Respiratory symptoms	**Total**	39 (58%)
	Cough	29 (43%)
	Rhinorrhea	18 (27%)
	Odynophagia	12 (18%)
	Chest pain	2 (3%)
	Difficulty breathing	4 (6%)
	Hypoxemia	0
Gastrointestinal symptoms	**Total**	29 (43%)
	Nausea	3 (4%)
	Vomiting	8 (12%)
	Diarrhea	14 (21%)
	Abdominal pain	12 (18%)
	Reduction of food intake	7 (10%)
Cutaneous manifestations	**Total**	5 (7%)
Musculoskeletal manifestations	**Total**	7 (10%)
	Myalgias	7 (10%)
	Arthralgia	1 (1%)
Neurological manifestations	**Total**	24 (36%)
	Irritability	3 (4%)
	Headache	20 (30%)
	Febrile convulsion	1 (1%)
Sensorial manifestations	**Total**	4 (6%)
	Anosmia	4 (6%)
	Dysgeusia	3 (4%)

phils) and three with a CRP slight elevation (0.85 mg/dL; 2.96 mg/dL and 12.86 mg/dL). No patient had leucopenia or lymphopenia. Three patients (4%), aged one, six and ten years old, underwent chest radiography (x-ray), and none of them had abnormalities suggesting COVID-19 pneumonia, instead the x-ray revealed peribronchial cuffing and perihilar interstitial thickening. No patient required a CT-scan.

Disease severity ranged from mild to slightly moderate, with no complication requiring support treatment (e.g., oxygen supplementation, ventilatory support, intravenous fluid) nor specific antiviral therapy. The majority of patients were discharged with only symptomatic measures with four children (6%) medicated with bronchodilators. Interventions such as hydration, antipyretics as needed and respiratory hygiene were recommended. Educational information on safety measures and disease prevention was provided, concerning disease prevention. Only one patient, an adolescent with a previous history of asthma, was transferred to a tertiary hospital due to respiratory distress. All the other patients (99%) were discharged home.

Follow-up was possible in 63 children (94%). All children were discharged by their family doctor after underwent a cure test, which happen after a median of 18.5 days. Nevertheless, all children became asymptomatic after average of 5 days. The patient transferred to the tertiary hospital was discharged after a 24-hour admission period, with acute symptomatic treatment.

Discussion

SARS-CoV-2 transmission occurs through close range contact, with infected droplets and aerosols, since these particles are inhaled or deposited on nasal, conjunctival or oral mucosa. Current evidence indicates that children appear to be less affected by COVID-19, in comparison with teenagers and adults, whether by staying asymptomatic (5%-23% according to international case series) or by experiencing milder disease, with limited impact on mortality. Nevertheless, in our study we did not have asymptomatic children, unlike the 20% asymptomatic patients reported in Hospital de Santa Maria (HSM) study in agreement with current evidence.[1,5]

Younger children in this study were less affected (only 5% below three months old and 16% below 12 months), compared with older children and adolescents. Infants and younger children seem to be less susceptible to infection, and when infected, less often lead to onward transmission than older children and adults.[6,7] Several hypotheses have been studied in order to explain this phenomenon: children have the ability to rapidly adapt to new pathogens, producing IgM at higher levels and a faster immune response; innate immunity at younger ages is better equipped at recognizing viral agents owing to community acquired viral infections and the use of vaccines; alveolar type II cells in children express lower quantities of ECA-2 receptor, through which the virus enters the epithelial and endothelial cells in the respiratory tract, replicating and causing damage; in children endothelial damage is practically absent, hence reducing the possibility of an exaggerated inflammatory response to SARS-CoV-2 infection; there are less comorbidities in children, comparing to adults, and they also have greater regenerative capacity.[8-10] Further studies are necessary to explore other possible causes.[8-10]

The median age of the infected children was six years, which is similar to the median found in HSM study (8 years) and in international literature (6.7 years).[1,5]

In our study, 58% of all children had a known history of high-risk contact with a positive case, which was less than the 83% found in HSM study – in both studies, nearly all positive contacts came from the same household. These findings are similar to those reported in international studies, where the COVID-19's incidence was higher within family clusters.[1,7]

Clinical manifestations in pediatric age can be similar to those of adults, with dominance of fever and upper respiratory tract symptoms, such as nasal congestion, anterior seromucous rhinorrhea and cough. In our study, fever and respiratory symptoms were observed more often comparing with HSM study (fever: 76% *vs* 43% and respiratory symptoms: 58% *vs* 42%). Myalgia (10% *vs* 6%), headache (30% *vs* 18%) and sore throat (18% *vs* 8%) are also frequently described in both studies and in international series. Children are more likely to suffer from gastrointestinal symptoms, such as abdominal pain, nausea/vomiting and diarrhea (43% in our study, 20% in HSM study),

than adults (15%).[1,5,7,11] Zhou *et al* found that SARS-CoV-2 uses angiotensin convertase enzyme (ACE2) as a cell entry receptor.[12] ACE2 is not only expressed in respiratory organs, but also in the digestive system and it is thought that SARS-CoV-2 may interact with ACE2 receptor in gastrointestinal tract, impair the intestinal mucous membrane barrier and increase the inflammatory cytokines production. Therefore, whether a higher rate of gastrointestinal symptoms in children group is related to higher expression of ACE2 in gastrointestinal tract or different functions of ACE2 is yet to be confirmed by further research.[12]

Olfactory and taste impairment associated with COVID-19 are less usual in childhood (6% in our study, 5% in HSM study *vs* 34 to 69% in adults).[1,13,14] The cutaneous manifestations in COVID-19 are diverse, comprising acral lesions, maculopapular, vesicular and urticaria-like exanthem, and the recently described "COVID-toes" (7% *vs* 5%).[1,15]

The BCG vaccine is aimed against tuberculosis, however there is evidence suggesting that it might provide protection against other diseases. At the beginning of the pandemic, it was postulated that BCG vaccination could provide protection against SARS-CoV-2 infection.[16] In our study we also looked for BCG vaccination history and, as in HSM study, we could not corroborate this theory.[1]

As for laboratory findings, COVID-19 in adults, usually causes significant abnormalities, beginning early in the disease.[7] In children however, laboratory tests are frequently normal, with occasional reports of neutropenia, lymphopenia and elevated CRP and procalcitonin levels.[7,17] In our study, laboratory testing was performed in 7% of the cases. Hospital de Santa Maria study had similar results, as they performed laboratory testing in only 9% of the cases.[1]

Similar to the laboratory findings, the majority of affected children do not present obvious findings on pulmonary imaging; when performed, frequently it reveals peripheral bilateral patchy opacities, peribronchial cuffing and ground-glass opacities.[7,17] In this series, three patients (4% *vs* 7% in HSM study),[1] aged one, six and ten years old, underwent chest radiography, showing peribronchial cuffing and perihilar interstitial thickening, hence none of them had abnormalities suggesting COVID-19 pneumonia.

Requesting diagnostic tests demands a careful consideration, particularly in children, and our procedure regarding chest radiograph is in line with the American College of Radiology recommendations that do not include chest x-rays as first line, in the management of a SARS-CoV-2 suspect or confirmed pediatric case, especially with mild disease.[18]

Occasionally, children, particularly those with risk factors, might develop moderate to severe disease, requiring hospitalization and support measures.[1,19] In a rare number of paediatric cases, an immune response is thought to be responsible for a particular situation of concern: the multisystem inflammatory syndrome in children (MIS-C), which involves the failure of two or more organs and comprises an elevated risk of death, even at younger ages. Currently, there is no sufficient evidence to identify those at risk for a worse outcome.[20,21]

Despite these rare severe cases, mortality rate in SARS-CoV-2 infected children is low, estimated to be under 1%.[19] In this sample almost all children had mild disease and only 6% had slightly moderate disease, with shortness of breath.

Available recommendations suggest that, whenever possible, patients should manage symptoms at home, using symptomatic treatment, after being provided with educational information on safety measures, concerning disease prevention and spread. According to national and international guidelines, antibiotics could be used if sepsis or clinical deterioration is suspected – which did not happen in our series.[17,19] Specific pharmacologic treatment is not yet approved, except Remdesevir for severe or critical disease in children older than 12 years old.[22]

Current literature shows that children often have a good prognosis, with milder symptoms and recovery one to two weeks, after the onset of the disease.[17] Long-term effects of SARS-CoV-2 infection in children are yet to be comprehended, however existing evidence suggests that unlike adults, children and young people appear to have a milder disease.[7] In this series, following a median of five days, all patients became asymptomatic. Until this date, none of the children included, reported the development of any kind of sequelae.

Conclusion

We conclude with this study, in agreement with previously published international and Portuguese pediatric case series, that children and especially adolescents are just as prone as adults to become infected with SARS-CoV-2 but are less likely to develop severe symptoms. The majority of infected children had a documented household contact, so it is important to teach and reinforce everyday preventive measures within family clusters. Our COVID-19 contingency plan was helpful in providing adequate clinical care for children and teenagers that attended our hospital emergency room with suspected or confirmed SARS-CoV-2 infection. All the cases diagnosed had a good follow-up (provided initially through telemedicine, via a hospital phone-call and followed by the family doctor through TRACE COVID platform). In this series, all had an excellent outcome, and none developed complications as pneumonia or MISC-C.

Nevertheless, with the present worsening of the pandemic, it is expected a rise in pediatric cases, so a greater understanding of this disease in this age group is paramount to further understand aspects of epidemiology, transmission in the community and guide clinical care.

Many aspects of this new disease remain unclear, so advances in prevention and effective management will require more investigation, as well as public health and government interventions.

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