Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Journal Scan

COVID-19 manifestations in children

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1. Article information

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2. Background

The coronavirus disease 2019 (COVID-19) has evolved into a global problem with diverse socio-economic and cultural implications. In a short duration of 6 months (mid December 2019 to June 2020) more than 10 million people have been infected with substantial mortality (4.18%). As on 20 July 2020, globally 14,538,094 confirmed cases, including 607,358 deaths have been reported to WHO (3.37 p.m., CEST).[1]

Most of the studies conducted till now have primarily focused on combined adult and pediatric populations. As the epidemic has climaxed at stage 3–4 in various countries, the numbers of children affected have also increased as reported in previous studies.[2] During the initial phase of the epidemic (December 2019 to March 2020) in various countries like China, Italy, Spain, UK and USA few children (<1%) were affected by the disease.[3,4] Most of the children were asymptomatic or had mild to moderate symptoms of infection. However as the pandemic spread to other countries in the developing world, more children became infected from their close contacts.[5] The Centers for Disease Control and Prevention, USA released an advisory on 14 May 2020 regarding severe multisystemic inflammatory response in children, based on a subset of children in a COVID-19 study. These children had presented with severe inflammatory response with multi-systemic failure.[6,7]

Various centers across the world have reported various manifestations like erythematous morbilliform skin rash, vesicular lesions, peeling of skin of digits of hands and feet (covid toes), utricaria, vasculitis and features resembling Kawasaki disease.[8,9]

A meta-analysis of various coronavirus studies related to the pediatric population has been recently published in the online version of E Clinical Medicine Journal (Elsevier Inc.) https://doi.org/10.1016/j.eclinm.2020.100433.

3. Summary

This is a systematic review of various clinical presentations, laboratory, radiological parameters and various modalities of treatment in 7780 pediatric patients incorporated in a meta-analysis from 26 centers across the world. The authors conducted an extensive literature search regarding pediatric population (0–21 years) related studies from various data bases like PubMed, Scopus, LitCovid and COVID-19 resources from various journals like Lancet, New England Journal of Medicine (NEJM), Journal of American Medical Association (JAMA) and the Chest and WHO-COVID-19 data bases. They identified 1142 records, 237 duplicate records were removed. Initial screening of 905 records was done; only 319 full text original articles were selected. All case reports, commentaries, editorials, reviews, health care guidelines, in-vitro experiments and molecular biology related articles were excluded from the analysis (n = 586).

Thus 319 eligible articles were selected for the analysis of data, 188 articles had insufficient information for data interpretation like pediatric data was not well defined from adults, COVID-19 uninfected neonates from perinatal exposure, articles from some languages could not be translated, one article was retracted and few news report articles were also excluded. Thus a final analysis (qualitative synthesis) of 131 articles was possible for interpretation of results. These studies were published between January 24, 2020 and May 11, 2020.

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All the patients included in the studies had evidence of COVID-19 infection, detected by presence of SARS-CoV-2 by real time RT-PCR from various biological samples at any time during the clinical course of illness.

3.1. Clinical and radiological findings

The primary aim of the study was to focus on various clinical manifestations, radiological findings and laboratory parameters of COVID-19 in children. They also identified various risk factors for development of complications like multi-systemic inflammatory syndrome in children (MIS-C) and need for subsequent intensive care. The criteria for diagnosis of MIS-C were as per the definition of CDC criteria i.e. fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem organ involvement (>2 systems) with no alternative diagnosis, and positive for SARS-CoV-2 infection.[5] Control group comprised of those patients who did not meet the criteria for MIS-C, chosen from the same case series of patients. All clinical, laboratory and radiological parameters were represented as median (IQR), mean (standard deviation), proportion or ratios where ever applicable. The statistical analysis between COVID-19 patients with and without multi-systemic inflammatory syndrome was calculated using STATA v-13 software.

In the final data analysis of 7780 patients from 131 studies (26 centers across the world) it was observed that 56% were males. Majority of the subjects were from China (64.1%) and USA (33%). The mean age of children was 8.9 years (SD 0.5). Approximately 75.6% of the subjects had a history of exposure to a family/household member, who was infected. Most of the children were not sick enough to warrant intensive unit care. They could be managed as out-patients or in-patients. Approximately 3.3% of the children were admitted in intensive care unit set ups. Only 0.54% (42 out of 7780) patients needed mechanical ventilation. The average hospital stay for available data of 662 patients was about 11.3 days.

Fever and cough were the two most predominant symptoms seen in 55.1% and 59.9% children respectively. However it was also observed that about 19.3% of children were asymptomatic and they were tested due to history of close contact. Rhinorrhea and nasal congestion was seen in 20% and sore throat was reported by 18.2% of the older children. The reported frequency of rhinorrhea was less in adults. Myalgia was observed in 18.7% of the patients. Shortness of breath or respiratory distress was observed in 11.7% in a cohort of 2445 patients. Other symptoms like diarrhea (6.5%), vomiting (5.4%), headache (4.5%) poor oral intake (1.7%), pharyngeal congestion (3.3%) were also noticed. Rash may be difficult to appreciate in Asian or African people, a miniscule population (0.5%) presented with rash.

It was observed that 35.6% (233 out of 655) children who were admitted had an underlying medical conditions like immunosuppression, cardiac conditions, respiratory diseases, endocrine/metabolic problems, hematological, prematurity related problems, obesity, renal diseases and gastrointestinal disorders.

A minority of children (72 out of 1183) who were infected with SARS-CoV-2 had co-infection with other respiratory pathogens like *Mycoplasma pneumonia*, respiratory, syncytial virus, influenza A and B, human metapneumovirus etc.

Abnormal radiographic findings were seen in 29.4% chest X-rays. In contrast 81.1% of the CECT (chest) done were abnormal with features of ground glass appearance, patchy infiltrates and consolidation seen in 556 out of 1115 CT scans evaluated. These subtle findings of CT scan have become a surrogate marker for diagnosis of COVID-19 infection in an epidemic scenario.

3.2. Laboratory findings

The hematological and biochemical laboratory findings of COVID-19 infection were no different from other respiratory viral infections. There was no evidence of leukopenia, the mean leukocyte count was 7.1×10^6 cells/L (SD 0.3). The C-reactive protein was mildly elevated 9.4 mg/L (SD 0.5) in a population of 643 patients. Other parameters that were elevated in the pediatric population were D-dimer 0.7 mg/L (SD 0.5), procalcitonin 0.25 ng/mL, IL-6 26.1 pg/mL (SD 3.7), CPK 197.9 units/L (SD 23.1). However there was no change in the values of LDH, ESR, serum ferritin and fibrinogen as compared to the normal reference range values for children.

One of the key observations of this study was children had less chances of developing complications of COVID-19 like pro-inflammatory processes like development of severe multi-systemic inflammatory response. Eleven patients (0.14%) confirmed to CDC criteria for definition of MIS-C.[5] Patients who were sick with inflammatory response had greater evidence of dyspnea, vomiting and diarrhea and leukopenia as compared to control group of 14 children. Serum lactate and D-dimer are prognostic markers for COVID-19 infection in children and were significantly elevated in the children with MIS-C ($p < 0.05$). The author analyzed the data for various clinical and laboratory parameters between children without and with multi-systemic inflammatory syndrome (MIS-C).

It is quiet striking that a comparative analysis of various laboratory parameters between COVID-19 children without and with features of MIS-C revealed a relative lymphopenia in the MIS-C group of children 11.1% versus 41.8% ($p < 0.01$). LDH and D-dimer were also significantly elevated in the MIS-C group. Other parameters like CRP, IL-2, IL-4, IL-6, IL-10 elevation implies pro-inflammatory response evoked by the viral pathogen. This may not be subtle to COVID-19 and could occur in other viral infections like SARS-CoV-1, dengue, RSV, influenza etc.

This trend of some abnormal laboratory findings is just an observation at present. We will need to have more studies to study the exact interpretation of these pro-inflammatory markers like IL-6, procalcitonin, CPK and D-dimer, to confirm if they are the real surrogate markers for development of MIS-C.

It is also clear that a number of antiviral drugs and immunomodulators have been used across various centers, depending on their individual preferences as there are no definite guidelines for use of these agents in children. In various studies an assortment of drugs like oseltamivir, interferons, intravenous immunoglobulin (IVIG), glucocorticosteroids, ribavarin for inhalational solution (Virazole®) and toclicizumab have been used in stable and sick patients who were admitted in the intensive care units. These “possible” SARS-CoV-2 agents have been used more frequently in sick patients.

4. Commentary

This is one of the largest meta-analysis (compilation of various COVID-19 related studies) which has been published till date with a large number of enrolled children (7782). It reaffirms the same finding that children tend to have less severe manifestations of COVID-19 as compared to adults. The number of infants, children and adolescents who need admission in hospitals or COVID-19 care centers are far less than the adults. This study has revealed that less than 3.5% of children who were admitted needed intensive unit care as compared to adults, which is about 25%. Seven deaths were reported in this study (mortality rate 0.09%); thus children tend to have fairly good prognosis following COVID-19. This is far less in comparison to the global crude fatality rate of 4.18% (WHO data as on July 20, 2020).[1]

In India the mortality rate in the total population is relatively low (2.43%) as compared to global figure of 4.18%.[10] The data of exact number of children affected by the infection and the mortality is not available in the public domain as of now.

According to the authors this study had its own limitations, like the data across different studies was not uniform. There was a lot of missing data in some studies like various biochemical, hematological or immunological parameters. The number of patients who developed complications like MIS-C is low; barely 11 patients have been identified from a large sample of 7782 patients.

This article has compiled all the possible relevant clinical, radiological and laboratory data in a comprehensive manner. As the disease progresses in various countries we will have more clinical and laboratory data available especially for risk of perinatal transmission in SARS-CoV-2 infection and infection in women. This is lacking at the present moment.

In the June 29, 2020 issue of NEJM, the authors (Leora R Feldstein et. al.) have described multisystem inflammatory syndrome in 186 children from 26 states in USA. These were children with serious illness which needed hospitalization. They had fever for more than 24 hours, multisystemic illness, SARS-CoV-2 PCR or antibody positivity or history of exposure in the past one month.

The presentations varied with features of shock and Kawasaki disease like features (coronary dilatations and aneurysms). They had elevated biomarkers of inflammation. All the children (median age 8.3 years) were previously healthy. MIS-C associated with this infection is potentially serious may require intensive care with mechanical ventilation, ECMO, inotropic support and various drugs like intravenous immunoglobulins, glucocorticoids and various immunomodulators like IL-6 and IL-1Ra inhibitors.[11]

Lately (June 19, 2020) an influenza drug favipiravir (FPR) for oral administration has been approved (restricted emergency use) for adults for mild to moderate severity of COVID-19 in India.[12] This can be used in patients with co-morbid illnesses like diabetes, immunosuppression, heart diseases or asthma. However this drug has not been approved in children below 18 years of age. FPR (Avigan)® is approved in Japan for treatment of influenza infection since 2014. Clinical trials of combination of favipiravir and umifenovir are being conducted in India by various pharmaceutical companies.

Another antiviral agent remdesivir (Gilead Sciences Inc.) for intravenous use was given emergency use authorization (EUA) by US Food and Drug Administration on May 1, 2020. It was initially developed as a drug for the treatment of Ebola infection following 2014 epidemic in few countries of Eastern Africa. It can be used for the treatment of suspected or laboratory confirmed cases of COVID-19. This is used in moderately to severely sick children and adults who are hypoxic, SaO2<94% in room air, need for oxygen supplementation or who need invasive or non-invasive modes of ventilation. The EUA approval was based on a clinical trial conducted by the National Institute of Health which has been published in May 22, 2020 issue of NEJM.[13] It has been also approved in UK, USA, Singapore, Japan and India.

Remdesivir was approved for emergency use in sick hospitalized patients by the Drug Controller General of India (DCGI) on June 1, 2020. This is available in the form of lypholized powder for injection (100 mg/vial) and remdesivir injection 100 mg/20 mL (5 mg/mL) in the form of solution. Various pharmaceutical companies in India are in the process of getting approval for marketing of this drug in India.

Declaration of competing interest

Authors have nothing to disclose.

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