Original Research Article

Clinical Profile Of COVID-19 Infection And SARS-Cov-2 IgG Antibody Response In Children Under 18 Years Of Age In A Tertiary Care Centre In North Kerala

Abstract

Background

The Global Pandemic Coronavirus disease ,was first reported in December 2019 in Wuhan and in March 11, 2020, got declared as global pandemic by World Health Organisation (WHO) . The morbidity and mortality of the disease have been rising with second wave of pandemic hitting worldwide.

Objectives:

To study the clinical profile of children under 18 years of age with COVID-19 infection and to study the IgG antibody response in covid infected children .

Materials and Methods

Children under 18 years of age except neonates who had COVID-19 infection and recovered from MMC Covid hospital were included for the study. After discharge blood samples were tested for COVID-19 IgG Antibody using SARS-CoV-2 IgG Reagent Kit 6R86 by Abbott Ireland diagnostics division . Data was entered into Microsoft excel sheet and statistical analysis done with SPSS VERSION 21.

Results

Children who fulfilled the inclusion criteria were taken up for the study. Median age in this study was 10 years .All affected children got infection from their family members. Fever as the presenting symptom were found in 62% children . Ninteen children showed positive IgG antibody and 2 out of 21 children showed negative IgG antibody level . There is significant association between IgG titre and timing of antibody testing after infection by the SARS-CoV-2 virus

Conclusion

Clinical profile and spectrum of COVID -19 infection were similar in all family members . Measures to prevent transmission of infection from family members to children will decrease infection by the SARS-CoV-2 virus in children. Antibody following infection by the SARS-CoV-2 virus will last only for few months ,making children susceptible to covid infection again. Vaccination among children is necessary to prevent rapid spread of covid infection.

Keywords - Clinical profile, COVID-19 Infection , IgG Antibody.

Introduction

The Global Pandemic Coronavirus disease(COVID-19), was first reported in December 2019 in Wuhan, China(1). On March 11, 2020, the World Health Organization declared COVID-19 as a global pandemic (2).By now COVID-19 infection is having an impact in all our lives. This viral infection has a wide variety of symptoms including cough, breathlessness, fever, chills, muscle pain, headache, sore throat, loss of smell or taste, and gastrointestinal symptoms. Clinical manifestations in patients were classified as mild, moderate, severe, and critically severe according to clinical diagnosis protocol (3,4).

SARS-CoV-2 is an enveloped, single-stranded RNA virus of the family Coronaviridae . This virus contains four structural glycoproteins: envelope (E), membrane (M), nucleocapsid (N), and spike (S) (5,6). Detection of SARS-CoV-2 viral RNA by reverse transcriptase polymerase chain reaction (RT-PCR) followed by a realtime PCR(QPCR) in samples collected from nasopharyngeal swabs or saliva is the gold standard diagnostic test to confirm early COVID-19 infection (7,8) . Detection of antibodies may further contribute to the identification of immune status of infected individuals(9,10)and improve the sensitivity of identifying children with asymptomatic infection . These antibodies have been reported to appear in serum or plasma of infected individuals after a few days to 2 weeks after the onset of symptoms(11). The sensitivity of combining viral RNA with antibody results has been reported as > 99%(10,11). The persistence of IgG antibodies allows identification of people who have been infected in the past, recovered from the illness, and possibly become immune(11).

IgG detection and other serological assays will play an important role in research and surveillance (12). Better understanding of humoral immunity after COVID-19 infection and the breadth of preexisting cross-reactive immunity will enable better treatment, diagnostic and vaccine strategies, which will help in controlling the current and future pandemics(13). The identification of these broad B and T cell epitopes with protective efficacy will serve as future targets for pancoronavirus vaccines and also predict disease severity after coronavirus infection(13). Currently, the antibody responses against SARS-CoV-2 remain poorly understood and the clinical utility of this serological testing is unclear especially in children (14). Very few studies are available in children with COVID-19 infection and antibody response . Hence to address this gap ,we conducted this cross sectional observational study to assess the clinical profile of COVID-19 infection and SARS –Cov2 IgG antibody response in children under 18 years of age in a tertiary care centre in north Kerala

Objectives

To study the clinical profile of children under 18 years of age with COVID-19 infection and to study the IgG antibody response in COVID-19 infected children .

Materials and Methods

This is an observational Study conducted in Malabar Medical College hospital and research centre , Modakkallur, Calicut,Kerala in November 2020 to March 2021.Inclusion criteria was children under 18years of age who had COVID-19 infection and recovered from Malabar Medical College Covid Hospital , Modakkallur .Neonates were not included in our study.

Data collection Methods and Data Analysis

All children with COVID-19 infection fulfilling the inclusion criteria were taken for the study .A detailed history and physical examination findings were assessed either from patient directly or from case sheets and was entered in a structured profoma .Detailed clinical history includes onset of symptom, duration of hospital stay ,comorbid conditions , presenting symptoms, and outcome and detailed physical examination includes general and systemic examination and nutritional assessment . All the patients were treated as per COVID-19 guidelines (5). After discharge all children were followed up for a period of 6 months . All the 21 patients (we communicated over phone and asked to come to hospital) were segregated into 5 groups (based on duration of recovery from COVID-19 into 1st ,2nd , 3rd , 4th and 5th month respectively) and tested for COVID-19 IgG Antibody by taking blood samples all at a time .During follow-up they were re-examined in detail and blood samples were collected for COVID- 19 IgG Antibody.

The SARS-CoV-2 IgG assay was done by an automated, two-step immunoassay, for the qualitative detection of IgG antibodies to SARS-CoV-2 in human serum and plasma using chemi luminescent microparticle immunoassay (CMIA) technology. Reagent used for the test was SARS-CoV-2 IgG Reagent Kit 6R86 by Abbott Ireland diagnostics division. The cut off value to call IgG titre as positive was 1.4 or more and titres less than 1.4 were reported as negative. The manufacturer's (Abbott Ireland diagnostics division) reported sensitivity is 84% if tested within 7 to 14 days and thereafter 100% and specificity is 99% .

Data collected was entered into Microsoft excel sheet and graphical and statistical analysis was performed with the help of statistical package for the social sciences (SPSS VERSION 21).Categorical variables were expressed as proportions and quantitative variables were expressed as median and interquartile range . Statistical test of significance −chi square test for categorical variables and Non parametric test using Mann-Whitney Test and Kruskal-WallisTest were used for quantitative variables.

Ethical Considerations : This study was reviewed and approved by Ethics Committee of our hospital.(No .MMC&RC/IEC/11/2020)

Results

During the study period total 36 covid positive children were admitted and treated in our hospital . Twenty one children who fulfilled the inclusion criteria were taken up for the study. Age distribution in this study was from 1year 6months to 17 years and median age was 10 years and inter quartile range (IQR) was 6.5 to 13 **Figure**(1).

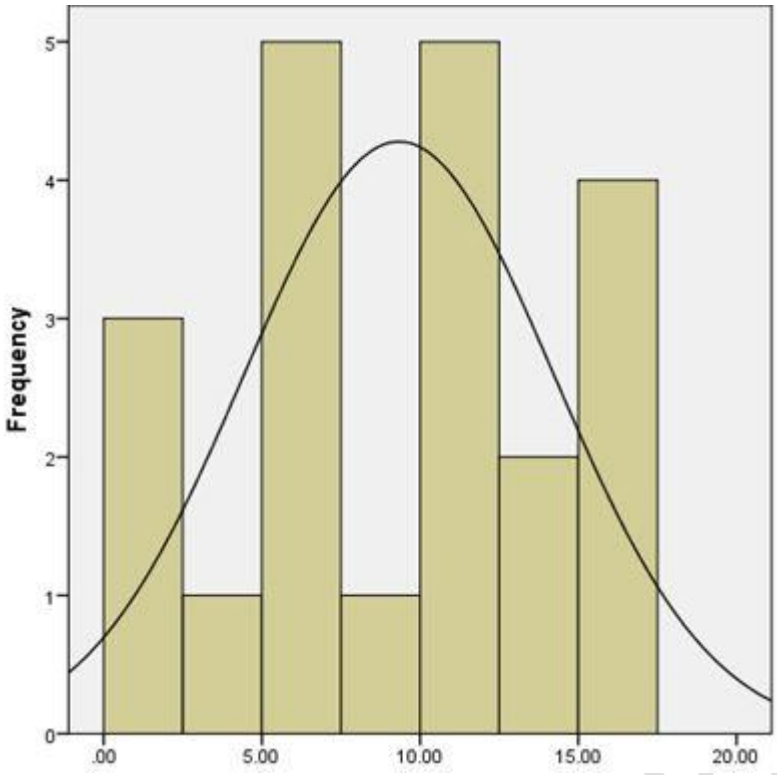

Figure (1) Age distribution in Histogram in our study population

In this study group 76% were boys and 24% were girls.Nutritional status of 71% children fell in between 3rd and the 50th percentile according to the IAP growth chart while 29% fell in between 75 and 97 percentile . Family members were the source of contact in all children . 76.2 % children did not have any comorbidities ,9.5% of children had bronchial asthma , and the others had allergic rhinitis(4.8%) ,migraine(4.8%), and seizures(4.8%) as comorbidities . No significant association was found between the severity of disease and comorbidities. 62% of patients had fever as the presenting or the first symptom while 14% had headache, 10% had upper respiratory infection symptoms as their presenting symptom (**Table1**).

First symptom or presenting symptom	Number of patients (n=21)	Percentage
Fever	13	61.9
Headache	3	14.3
URI	2	9.5
Asymptomatic	3	14.3
Total	21	100.0

Table 1 presenting symptoms

In this study 14.3% children were asymptomatic. Forty seven percentage of children were relieved of symptoms in 2 days , 9.6% within 4 to 5 days and 19% within 14 days. However 9.6% children took 1 to 2 months time for the relief of symptoms. None of the

patients in this study had severe morbidity or mortality .Average hospital stay in all children was around 10 days .This is because repeat COVID antigen test was done on the 10th day as per hospital policy . Even after becoming covid negative 14% of patients had symptoms like myalgia , tiredness and anosmia. We did not have any patient with multisystem inflammatory syndrome in children. Serum samples were collected over the course of six months to provide an information about SARS-CoV-2 serology responses.

Positive IgG antibody response seen in 19 children (90.5%) and 2 children (9.5%) showed negative IgG antibody response . Median IgG titre was 3.49 and inter quartile range (IQR) was 2.42 to 5.31 **Figure (2)**

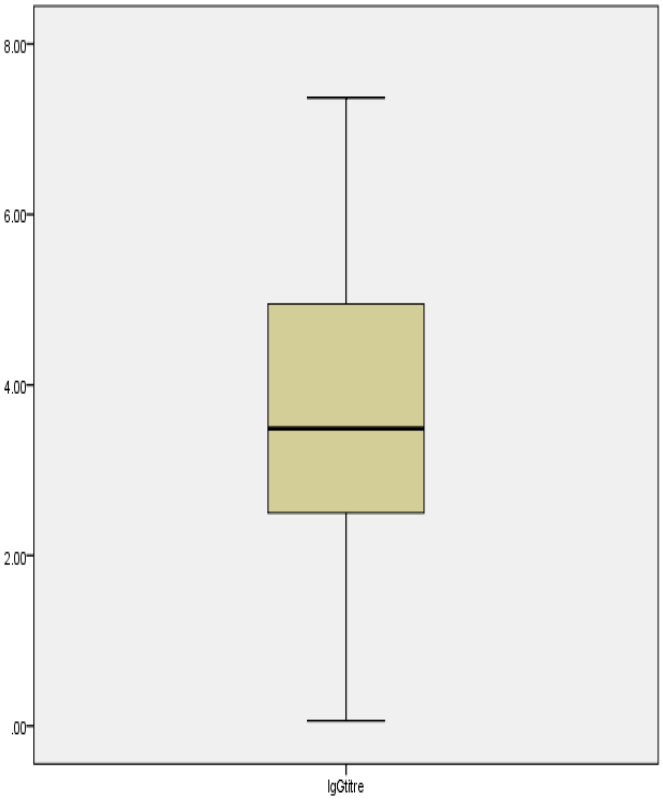

Figure (2) Box and whisker plot of IgGtitre showing antibody response to COVID 19

All the 21 patients (we communicated over phone and asked to come to hospital) were segregated into 5 groups (based on duration of recovery from COVID-19 into 1st ,2nd , 3rd , 4th and 5th month respectively) and tested all at a time. Children were tested for IgG antibody response at 1month were 9.5% ,33.5% at 2 months ,9.5% at 3 months, 19% tested at 4 months and 28.6% tested for antibody response at 5 months after COVID infection (table 2).

Timing of IgG antibody test after COVID-19 (in months)	Number of patients(n=21)	Percentage
1st	2	9.5
2nd	7	33.3
3rd	2	9.5
4th	4	19.0
5th	6	28.6
Total	21	100.0

Table 2 Timing of IgG antibody test after recovery from Infection by the SARS-CoV-2 virus

We found significant association between IgG titre and timing of of antibody testing after Infection by the SARS-CoV-2 virus according to Kruskal –Wallis test (P value – 0.032).After applying Post Hoc test in our study we got significant difference in IgG titre done at 1 month after Infection by the SARS-CoV-2 virus and IgG titre done at 5 months .There is significant reduction in antibody response after Infection by the SARS-CoV-2 virus as time progresses. Maximum IgG titre was 7.37 at 1 month after infection and minimum IgG titre was 0.06 at 3 months after infection. No significant association was found between IgG response and gender ,clinical symptoms,nutritional status, duration of hospital stay and post covid symptoms.

Discussion

Median age of patients in this study was 10 (IQR 6.5 -13) which is different from the study conducted by Christophers et al in which median age was 5years (IQR =8) (16).Out of 21 children with COVID-19 infection , fever was the most common presenting symptom . Other presenting symptoms were headache , cold ,cough and myalgia .

Eventhough 71.4% had fever ,only 61.9% of patients had fever as the initial presentation. Asymptomatic patients were 14.3%. In a study conducted by Christophers et al also shows similar results in which 62% of patient had fever at the time of presentation,32% had cough and 21% were asymptomatic(15) .We also noticed that initial Clinical symptom were the same in children and in all family members .Children were not the first symptomatic patient in any of the family . Family members might have received the infection from other adults.In our study we also noticed that none of these children were admitted in PICU and none of them had severe disease course although some of their family members had very severe disease .The exact mechanisms underlying the different SARS-CoV-2 immune responses based on age remain unclear. However , few possibilities have been suggested that children may have attenuated immune responses resulting in tolerance of the virus(16) . Some studies have suggested that the milder disease manifestations in children may be due to more active innate immune responses, healthier respiratory tracts due to less exposure to air pollution or cigarette smoke, and fewer comorbidities .Furthermore it has also been proposed that trained immunity may play a role

and that immune memory generated by other vaccines such as measles ,mumps, and rubella may confer a non specific protective immune response against SARS-CoV-2(17).

The reduced respiratory symptoms and low incidence of Acute Respiratory Distress syndrome (ARDS) in the pediatric age group suggest a distinct infection course, possibly due to lower expression of the viral receptor (angiotensin-converting enzyme 2 (ACE2) in pediatric airway epithelial cells or a more robust innate immune response in children(18) .

In this study most of the patients infected with SARS-CoV-2 have detectable SARS-CoV-2 IgG antibody. IgG antibody can be detected from serum after a period of 14 days after infection by the SARS-CoV-2 virus . In this present study IgG were detected to be elevated in 90% of patients. A study conducted by DeSimone Mia et al also showed 81.2% positive antibody response (19). In this study we noticed that there is significant reduction in IgG titre as time progresses especially after 3 months . A study conducted by BaweletaIsho et al also shows that serum and saliva IgG antibodies to SARS-COV-2 are maintained in the majority of COVID-19 patients for at least 3 months(20). Another study conducted by Yanan Wang et al showed that concentrations of IgG antibodies remained high for at least 3 months before subsequently declining(21) . These studies and the present study have raised the suspicion that SARS -CoV -2 immune response following natural infection may be short lived causing concerns about the durability of infection induced protection .

Conclusion

In this first wave of COVID-19 only few children were affected . All children got infection from their family members. So measures to prevent transmission of covid infection from family members to children has to be taken up seriously to decrease covid infection in children .

With this present study we would like to conclude that even post SAR-Cov-2 infection induces IgG antibodies against SAR-Cov-2 in majority of patients , antibody titre starts decreasing after a period of 2 months . Antibody following Infection by the SARS-CoV-2 virus will last only for few months ,making them susceptible to COVID-19 infection again .Hence vaccination among children is necessary to prevent rapid spread of COVID-19 infection.

Limitations

Twenty one is a small sample size . This is because only few children were affected in the first wave . Serial IgG monitoring would have been better to provide persistence of IgG antibody level in blood .

References

1. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med*. 2020; 382(13): 1199- 1207.
2. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19-11 March 2020. Accessed April 14, 2020. https://www.who.int/dg/speeches/detail/who-directorgeneral-s-opening-remarks-at-the-media-briefing-on-covid-19---11- march-2020

3. Chan JFW, Yuan S, Kok KH, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. 2020;395(10223):514- 523. doi:10.1016/S0140-6736(20)30154-9
4. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan,China.Lancet 2020;395(10223):497-506. doi:10.1016/S0140-6736(20)30183-
5. Covid -19 treatment guidelines for kerala state Ref No 31/F2/2020 H&FW dated 15th August 2020.
6. Gorbalenya AE, Baker SC, Baric RS, et al. The species severe acute respiratory syndrome related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol.2020;5(4):536-544. doi:10.1038/s41564-020-0695-z
7. Zhou P, Yang X Lou, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-273.doi:10.1038/s41586-020-2012-7
8. Pascarella G, Strumia A, Piliego C, et al. COVID-19 diagnosis and management: a comprehensive review. J Intern Med. Published online 2020:joim.13091. doi:10.1111/joim.13091
9. Zou L, Ruan F, Huang M, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. N Engl J Med. 2020;382(12):1177-1179. doi:10.1056/NEJMc2001737
10. Long Q-X, Liu B-Z, Deng H-J, et al. Antibody responses to SARSCoV-2 in patients with COVID-19. Nat Med. Published online 2020:1-4. doi:10.1038/s41591-020-0897-1
11. Jin Y, Wang M, Zuo Z, et al. Diagnostic value and dynamic variance of serum antibody in coronavirus disease 2019. Int J Infect Dis. 2020;94:49-52. doi:10.1016/j.ijid.2020.03.065
12. World Health Organization. Laboratory testing strategy recommendations for COVID-19: interim guidance, 21 March 2020. World Health Organization; 2020.
13. Fraley, E., LeMaster, C., Banerjee, D. *et al.* Cross-reactive antibody immunity against SARS-CoV-2 in children and adults. *Cell Mol Immunol* **18,** 1826–1828 (2021). https://doi.org/10.1038/s41423-021-00700-0
14. Tang, Y. W., Schmitz, J. E., Persing, D. H. & Stratton, C. W. The laboratory diagnosis of COVID-19 infection: current issues and challenges. J. Clin.Microbiol. https://doi.org/10.1128/JCM.00512-20
15. Christophers B, Gallo Marin B, Oliva R, Powell WT, Savage TJ, Michelow IC. Trends in clinical presentation of children with COVID-19: a systematic review of individual participant data. Pediatr Res. 2020 Sep 17:10.1038/s41390-020-01161-3. doi: 10.1038/s41390-020-01161-3. Epub ahead of print. PMID: 32942286; PMCID: PMC7965792
16. Elahi S. Neonatal and children's immune system and COVID-19: biased immune tolerance versus resistancestrategy. *J Immunol*. 2020;205(8):1990-1997. doi:10.4049/jimmunol.2000710
17. Yang HS, Costa V, Racine-Brzostek SE, et al. Association of Age With SARS-CoV-2 Antibody Response. *JAMA Netw Open*. 2021;4(3):e214302. Published 2021 Mar 1. doi:10.1001/jamanetworkopen.2021.4302
18. Weisberg, S.P., Connors, T.J., Zhu, Y. *et al.* Distinct antibody responses to SARS-CoV-2 in children and adults across the COVID-19 clinical spectrum. *Nat Immunol* 22**,** 25**–**31 (2021). https://doi.org/10.1038/s41590-020-00826-9
19. DeSimone, Mia, M.D., M.P.H, Simmons et al Clinical correlations of SARS-CoV-2 antibody responses in patients with COVID-19 infection ,medRxiv2020.10.22.20213207doi**:** https://doi.org/10.1101/2020.10.22.20213207

20. B. Isho et al.Persistence of serum and saliva antibody responses to SARS-CoV-2 spike antigens in COVID-19 patients, Sci. Immunol. 10.1126/sciimmunol.abe5511 (2020).
21. Wang Y, Li J, Li H, Lei P, Shen G, Yang C. Persistence of SARS-CoV-2-specific antibodies in COVID-19 patients. *IntImmunopharmacol*. 2021;90:107271. doi:10.1016/j.intimp.2020.107271