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Recent COVID-19 outbreak: effect in childhood

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ABSTRACT: The outbreak of 2019-novel Coronavirus disease (COVID-19) can be traced back to December 2019, when a cluster of patients with pneumonia of unknown etiology was found in Wuhan City, China. Diagnosis of COVID-19 may be challenging in children, since its clinical presentation overlaps with other viral upper and lower airways infections (i.e. influenza virus and respiratory syncytial virus), and they can occur as co-infection in/up to 40% of symptomatic cases. It has been observed a broad spectrum of clinical presentation for COVID-19, ranging from asymptomatic or mild to severe cases with severe acute respiratory distress, which may require intensive care. The aim of this paper is to provide an update on current data about COVID-19 in children.

Keywords: COVID-19, SARS-CoV-2, Children

Abbreviations: CL: Cutaneous Leishmaniasis; DAT: direct agglutination test; DCL: Diffuse cutaneous leishmaniasis; ELISA: enzyme-linked immunosorbent assay; HIV: Human Immunodeficiency virus; IFAT: Indirect fluorescent antibody test; kDNA: kinetoblast DNA; a network of ring-structured mitochondrial DNA; rK-39: rapid Kinesin protein of 39 amino acids; an antigen ok Leishmania major; rKE16: rapid Kinesin protein cloned in E. coli bacterium; MCL: Muco-cutaneous leishmaniasis; PCR: polymerase chain reaction; RNA: Ribonucleic acid; SSU PCR-OC: Small subunit ribosomal RNA-(18S rRNA) PCR-Oligochromatography; TTL: transfusion transmitted Leishmaniasis; VL: Visceral Leishmaniasis.

INTRODUCTION

The outbreak of 2019-novel Coronavirus disease (COVID-19) can be traced back to December 2019, when a cluster of patients with pneumonia of unknown etiology was found in Wuhan City, China. These cases were linked to the local seafood market and genome sequencing led to the identification of a novel Coronavirus (2019-nCoV)[1]. Recently, the International Committee on Taxonomy of Viruses (ICTV) renamed 2019-nCoV Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2)[2]. COVID-19 is the seventh member of the family of Coronaviridae, positive-sense RNA viruses, that infect humans and other mammals[1]. Other Coronaviruses caused previous outbreaks, such as Severe Acute Respiratory Syndrome (SARS-CoV) and Middle East Respiratory Syndrome (MERS)-CoV, occurred in 2002-2003 and 2012, respectively[3,4]. SARS-CoV-2 genome sequencing showed a greater homology with two bat-derived coronavirus strains rather than with known

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human-infecting coronavirus. Therefore, Lu et al[5] hypothesized that bats constituted reservoir for COVID-19. Nevertheless, they also stated that another wild animal may have acted as an intermediate host between bat and humans, before human-to-human transmission[5]. The outbreak of COVID-19 is becoming one of the greatest challenges for national health systems worldwide during last decades. Indeed, by 12 March 2020, 125,518 cases have been reported, including 4.617 lethal cases[6]. Many questions about COVID-19 are still unanswered, concerning transmission route, role of asymptomatic individuals in transmission, risk factors, case fatality ratio and optimal treatment. The aim of this paper is to provide an update on current data about COVID-19 in children.

TRANSMISSION

Person-to-person routes of transmission include respiratory droplet, close contact and contaminated hands[7]. Zhou et al[8] suggested that SARS-CoV-2 binds angiotensin converting enzyme 2 (ACE2) receptor for viral entry into cells, which is the source for viral replication[8]. ACE2 receptor is highly expressed in type 2 alveolar cells of lung. This can explain transmission route and why COVID-19 involves mainly lower airways. ACE2 receptor is also expressed in epithelial cells of tongue more than buccal and gingival tissues, and in various organs of the digestive system[9]. On this basis, fecal-oral transmission has been hypothesized as a possible transmission route[10]. Complications of the viral infections include acute respiratory distress syndrome, RNAemia, acute cardiac injury, and secondary infections[10]. Positive RT-PCR results on stool specimens was found in an asymptomatic child.[11]

CLINICAL PRESENTATION

It has been observed a broad spectrum of clinical presentation for COVID-19, ranging from asymptomatic or mild to severe cases with severe acute respiratory distress, which may require intensive care. Mean incubation period is estimated to be around 5.2 days (95% confidence interval 4.1-7.0)[12]. Data from the WHO-China Joint Mission on COVID-19 reported 55,924 confirmed cases, with a median age of 51 years. Among these, cases under the age of 18 years were 2.3%. Furthermore, 77.8% of cases were adults aged between 30-69 years. The most common clinical presentation included fever (87.9%), dry cough (67.7%), fatigue (38.1%), sputum production (33.4%), shortness of breath (18.6%), sore throat (13.9%). Other reported symptoms were headache (13.6%), myalgia or arthralgia (14.8%), chills (11.4%), nausea or vomiting (5%), nasal congestion (4.8%), diarrhea (3.7%), and hemoptysis (0.9%), and conjunctival congestion (0.8%)[13]. Upper airways symptoms (rhinorrhea, sneezing, or sore throat) were less frequent[14]. Case fatality ratio resulted higher in patients with comorbidities, such as cardiovascular disease or diabetes, and in the elders (21.8% of patients older than 80 years)[13]. These data and other reports led to speculate that children may be less susceptible to COVID-19 infection or develop a mild clinical course[12,15]. A possible explanation may be found in ACE2 receptors. Contrary to expectations ACE2 receptors expression decrease with increasing age in rat lungs[16]. Therefore, Lee et al[15] hypothesized that higher ACE2 receptors expression in children may have a protective role against lung injury, as evidenced by other studies on ACE2 and lung injury induced by respiratory viral infections. A small series of 20 children with COVID-19, 3 of whom were infants, reported fever in 60%, cough in 65%, nasal discharge in 15% and diarrhea in 15%[17]. A Chinese review, in which more than 230 individuals younger than 18 years with COVID-19 have been reported, showed that symptoms and their frequency in children are comparable to adults. Fever, fatigue and dry cough were the most common reported symptoms as clinical presentation. Gastrointestinal symptoms, mainly diarrhea, have been also reported, even if less frequently. Nevertheless, children seemed to develop a milder clinical manifestation than adults and respiratory distress occurred in coincidence with event of underlying conditions[18]. A retrospective study on 9 infected patients aged between 1 month and 11 months showed they have had at least an infected family member. Clinical presentation was fever in 4, mild upper respiratory tract symptoms in 2, no symptoms in 1 and missing data in 2[19]. Few data are available about newborns. It is still questioned whether a vertical transmission is possible. On a study of 10 neonates, born from mothers with COVID-19 infection, 6 developed respiratory distress. However, pharyngeal swab performed in 9 neonates, 7 of whom within 72 hours of life, resulted negative. This supports the idea that COVID-19 is not vertically transmitted, though false negative may not be ruled out, while respiratory distress may be due to maternal hypoxia related to COVID-19[20]. Furthermore, Chen et al[21] did not found COVID-19 in amniotic fluid, cord blood, neonatal throat swab, and breast milk samples collected from six neonates, born from mothers with COVID-19 pneumonia. None of neonates had asphyxia. To date, there are no cases of vertically transmitted infection reported in literature. Testing close contacts of COVID-19 patients gave the opportunity to evaluate COVID-19 positive asymptomatic cases. Hu et al[22] found that only 5 out of 24 asymptomatic cases developed symptoms, mainly mild, and individuals younger than 15 years tended to remain asymptomatic and with normal CT imaging. The authors also demonstrated asymptomatic carriers contribute to spread COVID-19 infection[22].

DIAGNOSIS

Diagnosis of COVID-19 may be challenging in children, since its clinical presentation overlaps with other viral upper and lower airways infections (i.e. influenza virus and respiratory syncytial virus), and they can occur as co-infection in/up to 40% of symptomatic cases[17]. Therefore, epidemiological history may be helpful to

identify suspected cases. This includes history of travel, residence in a cluster area or contacting patients with symptoms coming from a cluster area or contacting confirmed or suspected cases infected with COVID-19 within 14 days prior to disease onset. Epidemiological history should be related to clinical manifestations and/or radiological findings and/or laboratory examinations[23]. On admission, 86.2% of 1099 adults presented anomalies on chest CT scans, 56.4% ground-glass opacity and 51.8% bilateral patchy shadowing. Indeed, children also showed ground-glass opacities, while lung consolidation with surrounding halo sign can be considered as typical sign in children. Laboratory tests may show normal or reduced blood count and lymphocytopenia[17]. SARS-CoV-2 seems to induce increased levels of proinflammatory cytokines, among these IL-2 and TNF-α, which may play a role in the pathophysiology of lung inflammation and damage. Indeed, proinflammatory cytokines resulted higher in patients admitted to intensive care units[10].

Diagnosis is confirmed by real time PCR (RT-PCR) of throat swabs or, when feasible, sputum. However, RT-PCR may result negative in the early phase of disease[23]. Indeed, chest CT showed higher sensitivity, detecting radiological findings consistent with COVID-19 prior to positive RT-PCR[24].

TREATMENT

Currently, there are no effective or specific treatments for COVID-19. Treatment is supportive, based on non-invasive or invasive mechanical ventilation and oxygen supplementation in the event of respiratory distress. Antivirals, anti-inflammatory drugs, anti-ACE2 receptors, monoclonal antibodies and JAK-STAT inhibitors have been suggested as potential treatment and there are ongoing trials on antivirals[25-27]. At this moment, no vaccine is available and the whole population is susceptible to the infection. Therefore, primary prevention measures, based on promoting hygiene measures, restrictions of travel and movement of people, home isolation or hospitalization of confirmed cases and school closure, are crucial to prevent transmission. Early detection of COVID-19 should be another goal to contain the outbreak.

CONCLUSIONS

Children represent a small percentage of COVID-19 cases; therefore, they may be less susceptible. However, these assumptions are based on preliminary data and the pediatric cases are expected to increase, due to contact with infected adults in home setting. Children may have a remarkable role in the spreading of infection, especially because they develop mild or no symptoms. In this regard school closure may be a reasonable measure, but attention should be also given to the effects home confinement on children, which may have negative effects on behavioral and psychic conditions[28].

Further studies on large cohorts are needed to assess the impact of COVID-19 on children, its pathophysiology, clinical presentation and to find effective treatments.

Conflict of Interest:
The authors did not declare any conflict of interest

REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W for the China Novel Coronavirus Investigating and Research Team. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020; 382: 727-733.
2. Gorbalenya AE, Baker SC, Baric RS, de Groot RJ, Drosten C, Gulyaeva AA, Haagmans BL, Lauber C, Leontovich AM, Neuman BW, Penzar D, Perlman S, Poon LLM, Samborskiy DV, Sidorov IA, Sola I; Ziebuhr J for the Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol 2020. In press. doi:10.1038/s41564-020-0695-z
3. Peiris JSM, Guan Y, Yuen KY. Severe acute respiratory syndrome. Nat Med 2004; 10: s88-s97.
4. Zaki AM, Van Boheemen S, Bestebroer TM, Osterhaus ADME, Fouchier RAM. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med 2012; 367: 1814-1820.
5. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N, Bi Y, Ma X, Zhan F, Wang L, Hu T, Zhou H, Hu Z, Zhou W, Shao L, Chen J, Meng Y, Wang J, Lin Y, Yuan J, Xie Z, Ma J, Liu WJ, Wang D, Xu W, Holmes EC, Gao GF, Wu G, Chen W, Shi W, Tan W. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020; 395: 565-574.
6. European Centre for Disease Prevention and Control. https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases. Accessed 12 March 2020
7. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun 2020 Feb 26:102433. doi: 10.1016/j.jaut.2020.102433. [Epub ahead of print]8. Zhou P, Yang XL, Wang XG, Hu B, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Zhi ZL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020; 579: 270-273.
9. Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, Li T, Chen Q. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci 2020; 12: 8.
10. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu , Xiao Y, Goa H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497-506.
11. Tang A, Tong ZD, Wang HL, Dai YX, Li KF, Liu JN, Wu WJ, Yuan C, Yu ML, Li P, Yan JB. Detection of Novel Coronavirus by RT-PCR in Stool Specimen from Asymptomatic Child, China. Emerg Infect Dis 2020; 26(6). doi: 10.3201/eid2606.200301. [Epub ahead of print]
12. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KSM, Lau EHY, Wong JY, Xing X, Xiang N, Wu Y,

Li C, Chen Q, Li D, Liu T, Zhao J, Li M, Tu W, Chen C, Jin L, Yang R, Wang W, Zhou S, Wang R, Liu H, Luo Y, Liu Y, Shao G, Li H, Tao Z, Yang Y, Deng Z, Liu B, Ma Z, Zhang Y, Shi G, Lam TTY, Wu JYK, Gao GF, Cowling BJ, Yang B, Leung GM, Feng Z. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med 2020 Jan 29 doi: 10.1056/NEJMoa2001316. [Epub ahead of print]

13. Aylward B, Liang W. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf. Accessed 12 March 2020
14. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhy SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020 Feb 28. doi: 10.1056/NEJMoa2002032. [Epub ahead of print]
15. Lee PI, Hu YL, Chen PY, Huang YC, Hsueh PR. Are children less susceptible to COVID-19? J Microbiol Immunol Infect 2020 Feb 25. pii: S1684-1182(20)30039-6. doi: 10.1016/j.jmii.2020.02.011. [Epub ahead of print]
16. Xie X, Chen j, Wang X, Zhang F, Liu Y. Age-and gender-related difference of ACE2 expression in rat lung. Life Sc 2006; 78: 2166-2171.
17. Xia W, Shao J, Guo Y, Peng X, Li Z, Hu D. Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults. Pediatr Pulmonol 2020 Mar 5. doi: 10.1002/ppul.24718. [Epub ahead of print]
18. Lu Q, Shi Y. Coronavirus disease (COVID-19) and neonate: What neonatologist need to know. J Med Virol 2020 Mar 1. doi: 10.1002/jmv.25740. [Epub ahead of print]
19. Wei M, Yuan J, Liu Y, Fu T, Yu X, Zhang ZJ. Novel Coronavirus Infection in Hospitalized Infants Under 1 Year of Age in China. JAMA 2020 Feb 14. doi: 10.1001/jama.2020.2131. [Epub ahead of print]
20. Zhu H, Wang L, Fang C, Peng S, Zhang L, Chang G, Xia S, Zhou W. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. Transl Pediatr 2020; 9: 51-60.
21. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, Li J, Zhao D, Xu D, Gong Q, Liao J, Yang H, Hou W, Zhang Y. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet 2020; 395: 809-815.
22. Hu Z, Song C, Xu C, Jin G, Chen Y, Xu X, Ma H, Chen W, Lin Y, Zheng Y, Wang J, Hu Z, Yi Y, Shen H. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. Sci China Life Sci 2020 Mar 4. doi: 10.1007/s11427-020-1661-4. [Epub ahead of print]
23 Shen K, Yang Y, Wang T, Zhao D, Jiang Y, Jin R, Zheng Y, Xu B, Xie Z, Lin L, Shang Y, Lu X, Shu S, Bai Y, Deng J, Lu M, Ye L, Wang X, Wang Y, Gao L, China National Clinical Research Center for Respiratory Diseases, National Center for Children's Health, Beijing, China, Group of Respirology, Chinese Pediatric Society, Chinese Medical Association, Chinese Medical Doctor Association Committee on Respirology Pediatrics, China Medicine Education Association Committee on Pediatrics, Chinese Research Hospital Association Committee on Pediatrics, Chinese Non-government Medical Institutions Association Committee on Pediatrics, China Association of Traditional Chinese Medicine, Committee on Children's Health and Medicine Research, China News of Drug Information Association, Committee on Children's Safety Medication, Global Pediatric Pulmonology Alliance. Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts' consensus statement. World J Pediatr 2020. In press. doi:10.1007/s12519-020-00343-7
24. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, Tao Q, Sun Z, Xia L. Correlation of Chest CT and RT-PCR Testing in Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. Radiology 2020 Feb 26:200642. doi: 10.1148/radiol.2020200642. [Epub ahead of print]
25. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discov Ther 2020; 14: 58-60.
26. Stebbing J, Phelan A, Griffin I, Tucker C, Oechsle O, Smith D, Richardson P. COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect Dis 2020 Feb 27. pii: S1473-3099(20)30132-8. doi: 10.1016/S1473-3099(20)30132-8. [Epub ahead of print]
27. Maloney MA, Kun SS, Keens TG, Perez IA. Congenital central hypoventilation syndrome: diagnosis and management. Expert Rev Respir Med 2018; 12: 283-292.
28. Wang G, Zhang Y, Zhao J, Zhang J, Jiang F. Mitigate the effects of home confinement on children during the COVID-19 outbreak. Lancet 2020. Lancet 2020; 395: 945-947.