EXPERT REVIEW OF RESPIRATORY MEDICINE
https://doi.org/10.1080/17476348.2020.1761792

Taylor & Francis
Taylor & Francis Group

EDITORIAL

The challenge of resuming classes for young students in Wuhan, China

Rongrong Yang[a], Xien Gui[a], Yongxi Zhang[a]* and Yong Xiong[b]*

[a]Department of Infectious Diseases, Zhongnan Hospital, Wuhan University, Wuhan, China; [b]Department of Emergency, Zhongnan Hospital, Wuhan University, Wuhan, China

ARTICLE HISTORY Received 1 April 2020; Accepted 24 April 2020

KEYWORDS COVID-19; emerging infectious disease; asymptomatic; children; resuming classes; coronavirus

COVID-19 pneumonia is a newly recognized illness that has spread rapidly throughout Wuhan (Hubei province) to other provinces in China and around the world [1–3]. While swift isolation of individuals COVID-19 is at the core of the epidemic response of virtually all countries worldwide, it is likely that some asymptomatic patients, defined as those who do not show any relevant clinical symptoms, such as fever, cough, sore throat, and other self-perceived or clinically recognizable symptoms, but whose respiratory tract specimens test positive for COVID-19, are not captured in the established surveillance systems. Under the strict control of the Chinese government, Wuhan has had no new COVID-19 cases for several days since 18 March 2020, when both the new COVID-19 suspected cases and inventory COVID-19 suspected cases reduced to zero [4]. However, the spread of COVID-19 has not been effectively controlled in many other countries. As of April 17, in Wuhan, apart from the normal winter vacation, more than 2 months have passed since the regular date of resuming classes. When students can safely resume classes is a reference standard to evaluate the degree of threat to public health and to measure the effectiveness of controlling COVID-19 in China and around the world. As the first epicenter, Wuhan had the largest number of cases and potentially infected children in China, and their children have experienced the longest school closure in the world thus far. As more and more countries have closed their schools in facing COVID-19, the question of resuming classes for young children is relevant and important for not only Wuhan but also most countries affected by COVID-19. By analyzing the challenges of resuming school for children in Wuhan and targeted strategies, the original intention of this paper is to provide valuable experience for all children affected by the prevalence of COVID-19 all over the world.

Asymptomatic COVID-19 infections were previously reported in children [5–7]. One report about a familial cluster of COVID-19 found a 10-year-old boy had a positive result on qRT-PCR for COVID-19 and had ground-glass lung opacities identified by CT scan, whereas none clinical symptoms were observed during the whole hospitalization [5]. This study indicated that asymptomatic COVID-19 infection was possible. In another family cluster, three individuals were tested positive for COVID-19 infection on qRT-PCR, but two were asymptomatic patients [6]. This study hinted that asymptomatic COVID-19 patients might be overlooked by health-care professionals and thus unknowingly transmit the virus to others. On the basis of two reports on family cluster with COVID-19 infection (Family 1 and Family 2 shown in Table 1) [5,6], here, we reported another family cluster with COVID-19 asymptomatic infection (Family 3 shown in Table 1).

The father, a 38-year-old man, was a doctor working in a designated COVID-19 hospital since 21 January 2020. On Feb 10, he developed a fever of 37.8°C. Considering the COVID-19 outbreak and several colleagues had been infected with COVID-19, he underwent a series of tests related to COVID-19. The reports showed that he had a decreased lymphocyte count, abnormal chest CT images, and a positive result on qRT-PCR for COVID-19. The next day, as close contacts, his wife, his twins son and daughter were also screened for COVID-19. By contrast, they were all asymptomatic, with normal lymphocyte counts. All the serological indicators are shown in Table 2. The difference is that the wife and 7-year-old daughter had normal chest CT images but positive qRT-PCR for COVID-19, while the 7-year-old son had negative qRT-PCR for 4 times, but chest CT images showed typical findings-multiple patchy ground-glass shadows (Figure 1(a)).

It is interesting that the son had alanine aminotransferase (ALT) as high as 520 U/L and aspartate aminotransferase (AST) as high as 439 U/L when he was admitted to hospital on Feb 13. To identify the cause of liver damage, common etiological tests, including hepatitis a virus, hepatitis b virus, hepatitis c virus, hepatitis e virus, and EB virus, were all negative. Moreover, the child had not taken any medicine before the testing, including over the counter Chinese medicine. The oral Diammonium glycyrrhizinate enteric capsule was then taken to repair liver damage. During the period of isolation, an obvious process of changes on liver function tests of the son had been shown (Table 3). Throughout the course of the disease, the 7-year-old boy had a completely normal appetite. During the observation period from February 10 to February 29, the wife, the twins son and daughter in Family 3 still did not show any symptoms. The wife and the daughter both had negative qRT-PCR for COVID-19 on Feb 20 and Feb 17 (Table 4), respectively. By contrast,

CONTACT Yong Xiong yongxiong64@163.com Department of Infectious Diseases, Zhongnan Hospital, Wuhan University, Wuchang District, Wuhan 430071, China

*These authors contributed equally to this work.

Table 1. The characteristics of children with COVID-19 asymptomatic infection from three families.

	Family 1	Family 2	Family 3
Travel or exposure history	Travel from Shenzhen to Wuhan	Travel from Wuhan to Guangzhou	The father was a doctor working in a designated COVID-19 hospital
Exposure date	29 December 2019–4 January 2020	Jan 22–26 January 2020	Jan 21–11 February 2020
Family population	6	3	4
COVID-19 infected number	5	3	4
Asmptomatic cases	1	2	3
Asmptomatic person			
Family member	Grandson	Wife Son	Wife Son Daughter
Gender	Male	Female Male	Female Male Female
Age	10	33 3	37 7 7
Symptoms	None	None None	None None None
Routine blood test	Normal	Normal Normal	Normal Normal Normal
Chest CT	Manifestation of viral pneumonia	Normal Normal	Normal Manifestation of viral pneumonia Normal
Nasopharyngeal or Throat Swab	Positive	Positive Positive	Positive Negative Positive

Table 2. The initial laboratory features of three asymptomatic patients in family 3 on admission.

	Son	Daughter	Normal range	Wife	Normal range
White blood cell count, $\times10^9$/L	4.79	6.86	3.85–10.5	6.89	3.5–9.5
Neutrophil count, $\times10^9$/L	2.23	1.47	1.08–5.9	4.8	1.8–6.3
Lymphocyte count, $\times10^9$/L	2.18	4.66	1.15–6.0	1.27	1.1–3.2
Monocyte count, $\times10^9$/L	0.32	0.49	0.26–0.8	0.76	0.1–0.6
Red blood cell count, $\times10^{12}$/L	4.59	4.36	3.5–5.3	4.08	3.8–5.1
Hemoglobin, g/dL	129.9	120.8	110–160	136.9	115–150
Platelet count, $\times10^9$/L	279	355	100–378	226	125–350
Prothrombin time, sec	13.1	12.4	9.4–12.5	12.0	9.4–12.5
Activated partial thromboplastin time, sec	36.7	36.3	25.1–36.5	30.3	25.1–36.5
Creatine kinase (CK), U/L	78	45	<171	70	<171
Lactatc dchydrogenase (LDH), U/L	391	209	125–243	180	125–243
Alanine aminotransferase (ALT), U/L	520	16	9–50	20	7–45
Aspartate aminotransferase (AST), U/L	439	24	15–40	16	13–35
Total bilirubin, μmol/L	8.7	10.5	5–21	12.6	5–21
Urea, mmol/L	6.85	3.16	2.8–7.6	4.24	2.8–7.6
Creatinine, μmol/L	37.4	28.9	64–104	53.1	49–90
C-Reactive Protein (CRP), mg/dL	0.4	0.4	0–10	2.0	0–10
Procalcitonin, ng/mL	<0.05	<0.05	<0.05	<0.05	<0.05
Erythrocyte sedimentation rate (ESR), mm/h	2	5	0–20	7	0–20

the son always had negative qRT-PCR for COVID-19 until Feb 22 (Table 4), but chest CT images showed that the lung lesions were basically absorbed and slight fibrosis were occurred (Figure 1(b)).

The above three different families show a common characteristic. That is, throughout the course of COVID-19 infection, the children did not have any clinical symptoms. There is accumulating evidence indicating that a substantial fraction of COVID-19-infected individuals are asymptomatic [8–12], especially in children aged 0–14 years [5–7,13]. The estimated asymptomatic proportion were 17.9% [9] and 16.7% [10] in two studies, respectively. Considering the reported similarity in viral loads between asymptomatic and symptomatic patients [14] and that transmission of COVID-19 by asymptomatic cases may be possible. Later, a study on a familial cluster of five patients with COVID-19 infection in Anyang, China, confirmed that the coronavirus may have been transmitted by the asymptomatic carrier [15]. Another epidemiological study found that COVID-19 infection rates among close contacts of asymptomatic and symptomatic COVID-19 patients were 4.11% (6/146) and 6.3% (126/2001), respectively, which showed no statistical difference [10].

A recent research pointed out that substantial undocumented infection facilitates the rapid dissemination of COVID-19 [16]. In preparation for the resumption of classes, the contagious of COVID-19 asymptomatic infection children should be paid special attention to avoid second outbreak of the disease.

Moreover, there are some clues but inconclusive findings about the characteristics of asymptomatic COVID-19 infection children. Such as the 7-year-old boy in Family 3, although it was not clear that the liver damage in this child was caused by COVID-19 infection, the possibility cannot be ruled out at least. Liver damage has been reported in symptomatic COVID-19 patients [17–20], but such severe and reversible liver damage

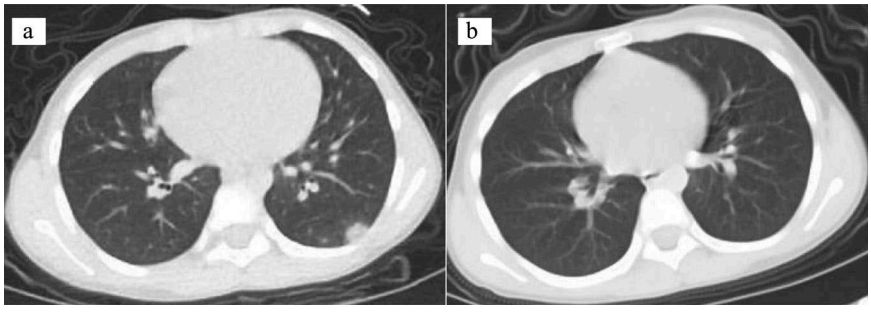

Figure 1. Chest computed tomographic images of the 10-year-old son in family 3 during hospitalization. (a) was the chest CT images on day 1 of admission, it showed a bilateral distribution of patchy shadows. (b) showed significant lesion absorption on day 12 of admission comparing to the same level images of (a).

Table 3. The tend of liver function of the son in family 3 during hospitalization.

	Admission day										
	1	2	3	4	5	6	7	8	9	10	Normal range
Alanine aminotransferase (ALT), U/L	520		279		137					44	9–50
Aspartate aminotransferase(AST), U/L	439		70		34					22	15–40
AST/ALT	0.84		0.25		0.25					0.5	0.2–2.0
Total bilirubin, umol/L	18.5		8.7		6.3					8.3	5–21
Direct bilirubin, umol/L	3.8		1.7		1.6					2	0–7
Indirect bilirubin, umol/L	14.7		7		4.7					6.3	1.5–18
Albumin, g/L	44.5		39.4		37.8					37.4	40–55
Globulin,g/L	25.2		23.1		20.2					21.3	20–30
A/G	1.77		1.71		1.87					1.76	1.5–2.5
	Began to take oral Diammonium glycyrrhizinate enteric capsule to repair liver damage.										

Table 4. Evolution pattern of SARS-CoV-2 RNA positivity among three asymptomatic patients with COVID-19 in family 3 during hospitalization.

		Admission day											
	Sample	1	2	3	4	5	6	7	8	9	10	11	12
Son	NPS	Δ			Δ		Δ	Δ				Δ	
Daughter	NPS	■		■				Δ	Δ				Δ
Wife	NPS	■			■		■		◎		Δ		Δ

Abbreviations: NPS: nasopharyngeal swab; ■: Positive; Δ: Negative; ◎: Inconclusive.

in asymptomatic patients has not been reported. In addition, COVID-19 can bind to their target cells through angiotensin-converting enzyme 2 (ACE2), which can be expressed by testis [21–23]. Whether this theoretical combination of virus and target cells affects testicular function is still unknown and needs further investigation.

In view of the occult, infectious, disease diversity, and uncertainty damage to testis of COVID-19 asymptomatic infected children, the safe time of resuming classes in high-incidence areas must be carefully evaluated. Otherwise, once an outbreak occurs in schools where the population is concentrated, it will spread much faster than in communities. How to avoid the resumption of classes leading to the second epidemic outbreak of COVID-19 is an urgent problem to be solved. In our opinion, the next stage of COVID-19 prevention and control needs to focus on the screening of asymptomatic population in the community. Before the school is ready to resume classes, children should be closely monitored and examined for nucleic acid testing of COVID-19 to rule out asymptomatic infection, even if they do not have any symptoms. There is no doubt that the economic cost of COVID-19 screening is considerable. Different countries may need to further balance the input-output ratio according to their national conditions.

There were some limitations in this study. First, the 7-year-old boy in Family 3 presented with typical viral pneumonia, but the cause of the negative results of viral nucleic acid is unclear. The possibility of poor technique of nasopharyngeal swab collection and PCR detection for SARS-CoV-2 nucleic acid are excluded, because his sister and mother were operated by the same nurse and laboratory technician. It is also unlikely that the boy was infected with mutated SARS-CoV-2, because his sister, his mother, and he were all close contacts with his father. The low sensitivity of the test reagent may be the reason for the negative result, so it is necessary to improve the sensitivity of the test kit. Second, alternative samples for detection of SARS-CoV-2 (such as stool) were not collected as medical resources are extremely limited at the early stage of COVID-19 outbreak in Wuhan. Simultaneous testing of multiple samples may be an effective measure to decrease the occurrence of false-negative results. Moreover, repeated testing of lower respiratory tract samples are warranted in clinically suspected cases with an initially negative result in nasopharyngeal swab.

Based on our data on SARS-CoV-2 RNA shedding in stool and the possibility of a lag in viral detection in nasopharyngeal swab specimens, the assessment of both fecal and respiratory specimen is recommended to enhance diagnostic sensitivity, and also to aid discharge decision before the role of viral RNA shedding in stool is clarified.

Funding

This work was supported by Medical Science Advancement Program (Basical Medical Sciences) of Wuhan University, Grant [NO.TFJC2018002].

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

RY conceived the study. RY and YX wrote the protocol. YZ performed the literature search. RY and YZ performed the statistics and drafted the first manuscript. XG and YX critically revised the manuscript. All authors reviewed and approved the final manuscript.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727–733.
2. 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. published online Jan 24.

3. Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med. 2020;382(10):929–936. published online Jan 31.
• **The report about the first case of COVID-19 in United States.**
4. National health commission. Latest outbreak: 34 new confirmed COVID-19 cases in China as of 24:00 on March 18. 2020 Mar 19. Available from: http://dezhou.iqilu.com/dzminsheng/2020/0319/4494510.shtml
5. Chan JF, 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;395:514–523.
• **The report about asymptomatic child with SARS-CoV-2 infection in a family cluster cases.**
6. Pan X, Chen D, Xia Y, et al. Asymptomatic cases in a family cluster with SARS-CoV-2 infection. Lancet Infect Dis. 2020 Feb 19;20(4):410–411.
• **The report about asymptomatic child with SARS-CoV-2 infection in another family cluster cases.**
7. Qiu H, Wu J, Hong L, et al. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. Lancet Infect Dis. 2020 Mar 25.
•• **An important article on the analysis of children with SARS-CoV-2 infection in China.**
8. Du Z, Xu X, Wu Y, et al. Serial interval of COVID-19 from publicly reported confirmed cases. Emerg Infect Dis. 2020;26. DOI:10.3201/eid2607.200357
9. Kenji M, Katsushi K, Alexander Z, et al. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. Euro Surveill. 2020;25(10):pii=2000180.
10. Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. Zhonghua Liu Xing Bing Xue Za Zhi. 2020;41(2):145–151. PMID: 32064853.
11. Hoehl S, Rabenau H, Berger A, et al. Evidence of SARS-CoV-2 infection in returning travelers from Wuhan, China. N Engl J Med. 2020;41(2):NEJMc2001899. PMID: 32069388.
12. 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. PMID: 31986264.
13. Liu W, Zhang Q, Chen J, et al. Detection of COVID-19 in children in early January 2020 in Wuhan, China. N Engl J Med. 2020;382(14):1370–1371.
14. 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;41(2):NEJMc2001737. PMID: 32074444.
•• **An important article to compare SARS CoV-2 viral load in upper respiratory specimens of symptomatic and asymptomatic patients.**
15. Bai Y, Yao L, Wei T, et al. Presumed asymptomatic carrier transmission of COVID-19. JAMA. 2020;323(14):1406–1407.
16. Li R, Pei S, Chen B, et al. Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV2). Science. 2020;eabb3221. DOI:10.1126/science.abb3221
17. Fan Z, Chen L, Li J, et al. Clinical features of COVID-19-related liver damage. Clin Gastroenterol Hepatol. 2020 Apr 10. pii: S1542-3565(20)30482-1. DOI:10.1016/j.cgh.2020.04.002
18. Liu C, Jiang ZC, Shao CX, et al. Preliminary study of the relationship between novel coronavirus pneumonia and liver function damage: a multicenter study. Zhonghua Gan Zang Bing Za Zhi. 2020 Feb 20;28(2):148–152. [Chinese].
19. Feng G, Zheng KI, Yan QQ, et al. COVID-19 and liver dysfunction: current insights and emergent therapeutic strategies. J Clin Transl Hepatol. 2020 Mar 28;8(1):18–24.
20. Hu LL, Wang WJ, Zhu QJ, et al. Novel coronavirus pneumonia related liver injury: etiological analysis and treatment strategy. Zhonghua Gan Zang Bing Za Zhi. 2020 Feb 20;28:E001.
21. Fan C, Li K, Ding Y, et al. ACE2 expression in kidney and testis may cause kidney and testis damage after 2019-nCoV infection. medRxiv. 2020 Dec 2;20022418. DOI:10.1101/2020.02.12.20022418
22. Wang Z, Xu X. scRNA-seq profiling of human testes reveals the presence of ACE2 receptor, a target for SARS-CoV-2 infection, in spermatogonia, leydig and sertoli cells. Preprints. 2020;2020020299. DOI:10.20944/preprints202002.0299.v1
23. Zhao Y, Zhao Z, Wang Y, et al. Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCoV. bioRxiv. 2020 Jan 26;919985. DOI:10.1101/2020.01.26.919985