Clinical analysis and early differential diagnosis of suspected pediatric patients with 2019 novel coronavirus infection

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Abstract

Background: Early differential diagnosis of suspected pediatric patients is difficult during the 2019-nCoV epidemic.

Objective: To identify clinical characteristics and key points of early differential diagnosis.

Methods: A retrospective analysis was performed on suspected pediatric cases.

Results:A total of 77 suspected cases were admitted from Jan 22nd to Mar 1st. Compared with non-2019-nCoV group (n=33),2019-nCoV confirmed group (n=35) had fewer fever (OR[95% CI] 0.39[0.242–0.628];P<.001) and symptoms of ARI (0.454[0.287–0.719];P<.001),more asymptomatic (15.086[2.117-107.475];P<.001), and more family cluster infections (5.469[2.405-12.433]; P<.001),while chest CT had more positive findings of viral pneumonia (1.813[1.131-2.908];P=.014).There were significant statistical differences between the two groups in age (7.2[3.9-11.4] vs 5[2.1-7.8];P=.031),body temperature (36.7[36.2-36.9] vs 37[36.7-37.9];P=.001), heart rate ([97.1±16.8] vs [109.7±15.6];P=.002),percentage ([39.4±14.9] vs [52.5±17.5]; P=.001) and count (2.25[1.43-3.53] vs 3.33[2.8-5.18];P=.007) of neutrophil, percentage (45.3[39.2-56.6] vs 33.2[22.7-42.5];P=.001) of lymphocyte,hs-CRP (5.52[1.1-9.04] vs 9.04[7.35-9.54];P=.002) and PCT (0.05[0.03-0.08] vs 0.1[0.05-0.21];P<.001),while gender (42.9% vs 57.6%;P=.332),respiratory rate (22[20-22] vs 22[20-24];P=.092),WBC (5.37[4.67-8.08] vs 6.94[5.72-8.87];P=.198), lymphocyte count (2.68[1.99-4.01] vs 2.26[1.66-2.92];P=.096),Hb (128[124-142] vs 130[119-137];P=.572) and PLT ([279.1±77.5] vs [263.4±65.1];P=.37) were statistically insignificant.

Conclusions: Asymptoms or mild symptoms,positive CT findings and family cluster infection are the main clinical characteristics of infected pediatric patients. The CBC, hs-CRP and PCT can provide an important basis for early differential diagnosis. Compared with other non-bacterial infections,hs-CRP and PCT in 2019-nCoV infection are reduced,but further evidence is needed to support whether their reduction is specific.

Keywords: 2019 novel coronavirus;acute respiratory infection; pediatric;differential

diagnosis;suspected infection.

Abbreviations:2019-nCoV,2019 novel coronavirus;CT,computed tomography; RT-PCR,real-time reverse transcriptase polymerase chain reaction;IQR,interquartile range;OR,odds ratio;CI,confidence interval;SD,standard deviation;ARI,acute respiratory infection; CAP,community-acquired pneumonia;RSV, respiratory syncytial virus; MP, mycoplasma pneumoniae; INF A,B,influenza A,B;CBC,complete blood count;WBC,white blood cell;N%, percentage of neutrophil; L%, percentage of lymphocyte; Hb, Hemoglobin;PLT, platelet; hs-CRP,high sensitivity C-reactive protein; PCT, procalcitonin.

Introduction

Children are naturally susceptible to various respiratory viruses due to their imperfect immune functions.Since the outbreak of 2019-nCoV began in Wuhan city,Hubei province,China.[1-2] more than 2,000 pediatric cases have been reported nationwide in just over two months.[3] Limited by accuracy of nucleic acid detection,[4] relative reagent shortage and non-specificity of imaging findings,[5] early differential diagnosis of suspected pediatric patients with 2019-nCoV infection is difficult to some extent.Obviously,this has a serious impact on timely triage,the following reasonable treatment,early removal of isolation, and improvement of psychological stress in children.

At present, a growing number of studies have focused on diagnosis and treatment of confirmed cases, but few data are available on clinical characteristics and early identification of suspected pediatric patients with 2019-nCoV infection as a special population. We aimed to investigate and identify the clinical characteristics and explore the key points of early differential diagnosis, so as to provide a basis for the follow-up timely and reasonable treatment and effective implementation of prevention and control measures.

Materials and Methods

Definition and classification

Children are defined as being less than 18 years old. Referring to the guidelines on the diagnosis and treatment of 2019-nCoV infected pneumonia (the sixth edition draft) issued by the National Health Commission of China.[6-7] Suspected cases are defined as having a clear epidemiological exposure, with or without clinical manifestations, and with or without positive CT findings.Epidemiological exposure includes close contact with confirmed cases,and or living or traveling in endemic areas (especially Hubei province), and or presence of confirmed case in their residential communities. If nasopharyngeal swab or anal swab specimens tested positive for 2019-nCoV nucleic acid using RT-PCR assay,suspected case is identified as a confirmed case. Fever was recognized when body temperature is higher than or equal to 37.3□.Symptoms of ARI includes nasal congestion, runny nose,

sneezing,sore throat, cough, expectoration, chest pain,dyspnea,etc.All chest CT images were reviewed by two experienced pediatric radiologists. If unilateral or bilateral lung fields have any of the features as follows:(a) ground glass opacities;(b) consolidations with surrounding halo sign;(c) nodules;(d) residual fiber strips;(e) lymphadenopathy.The result is defined as positive CT findings of viral pneumonia.[5,8-9] Family cluster infection was defined as the occurrence of any of the following criteria in 2 or more family members within a period of less than 1 week: (a) fever;(b) symptoms of acute respiratory tract infection;(c) positive CT findings of viral pneumonia.

Data collection

We conducted a retrospective study on all clinical and laboratory data. From Jan 22nd to Mar 1st,all suspected pediatric patients were admitted to the national clinical center of infectious diseases of the third People's Hospital of Shenzhen,and relevant examinations were completed as routine precedures, and clinical and laboratory data of the first day after admission were collected. Based on laboratory pathogen identification results including 2019-nCoV,INF A,INF B,RSV,MP, and bacteria,all cases were divided into the 2019-nCoV confirmed group and the non-2019- nCoV group, and the differences between the two groups were compared.

Inclusion criteria: all suspected pediatric cases.

Exclusion criteria:(a) pathogen identified as bacteria or MP; (b) coinfection; (c) PCT > 0.5 ng/mL.[10]

Statistical Analysis

All analyses were conducted by using of IBM Statistical Product and Service Solutions software Version 24 (SPSS Inc,Chicago,IL).Continuous variables were summarized as the median with their IQRs or mean with SDs, median [IQR] or [mean ±SD], depending on whether their distributions were normal or not.Comparisons of categorical variables were performed using the Pearson Chi□square test.The parametric tests (independent sample Student t-test) or non-parametric tests (Mann-Whitney U test) were used to analyse variables. P <.05 was considered as statistically significant in all tests if applied.

Results

From Jan 22nd to Mar 1st, a total of 77 suspected pediatric patients were admitted, and 39 (50.6%) were confirmed with 2019-nCoV infection, including 3 (3.9%) cases of RSVcoinfection, and 1 (1.3%) case with INF B coinfection.5(6.5%) of 38 (51.6%) cases of non-2019-nCoV infection were excluded by laboratory results and CT scan,consisting of 3 (3.9%) cases with PCT greater than 0.5ng/mL,were considered as bacterial infection,and 2 (2.6%) cases were considered as MP coinfection.The including 33 (42.9%) patients consisted of 3 (3.9%) cases of INF A, 2 (2.6%) cases of INF B, 9 (11.7%) cases of RSV and 19 (18.2%) cases of unidentified non-bacterial pathogens (details of excluded cases in Supplement Table 1).

Compared with non-2019-nCoV group (n=33),2019-nCoV confirmed group (n=35) had fewer fever (OR[95% CI] 0.39[0.242–0.628];P<.001) and symptoms of ARI (OR[95% CI] 0.454[0.287–0.719];P<.001),more asymptomatic (OR[95%CI]15.086 [2.117-107.475]; P<.001),and more family cluster infections (OR[95% CI] 5.469[2.405-12.433]; P<.001),while chest CT had more positive findings of viral pneumonia(OR[95%CI] 1.813[1.131-2.908];P=.014).There were significant statistical differences between the two groups in age (7.2[3.9-11.4] vs 5[2.1-7.8];P=.031),body temperature (36.7[36.2-36.9] vs 37[36.7-37.9];P=.001), heart rate ([97.1±16.8] vs [109.7±15.6]; P=.002),percentage ([39.4±14.9] vs [52.5±17.5];P=.001) and count (2.25[1.43-3.53] vs 3.33[2.8-5.18];P=.007) of neutrophil,percentage (45.3[39.2-56.6] vs 33.2[22.7-42.5];P=.001) of lymphocyte, hs-CRP (5.52[1.1-9.04] vs 9.04[7.35-9.54]; P=.002) and PCT (0.05[0.03-0.08]vs 0.1[0.05-0.21]; P<.001),while gender (42.9% vs 57.6%;P=.332),respiratory rate(22[20-22] vs 22[20-24];P=.092),WBC(5.37[4.67-8.08] vs 6.94[5.72-8.87]; P=.198),lymphocyte count(2.68[1.99-4.01] vs 2.26[1.66-2.92];P=.096),Hb (128[124-142] vs 130[119-137];P=.572) and PLT([279.1±77.5] vs [263.4±65.1];P=.37) were statistically insignificant (details in Table 1).

Discussion

Every winter and spring, a variety of virus infections are prevalent worldwide,[11] such as parainfluenza,RSV, INF A and B,rhinovirus and cytomegalovirus,etc.[12-14] A

significant number of CAP are caused by viruses, either directly or as part of a coinfection. The clinical picture of these different pneumonias can be very similar, but viral infection is more common in the pediatric populations.Despite great advances in virus detection and pneumonia imaging,[4-5] the identification and differential diagnosis of viral infections has been facing enormous challenges because laboratory detections and radiographic images are not always in agreement with clinical features and contact histories of patients.[15-17] RT-PCR methods based on spike gene and N gene were widely used for detecting viral RNA,and were considered a gold standard.[18-19] However, this method had its limitations, such as false positive or false negative results,time consuming,false sampling,inconsistence of sample collections and preparations. Most importantly, the inaccuracy of RT-PCR method caused problems in timely triage,isolating the source of infection,the following reasonable treatment, early removal of isolation, and improvement of psychological stress in children.[20] In addition, CT changes in novel coronavirus viral pneumonia are nonspecific and difficult to differentiate from other viral infections.[8-9,17] Therefore, it is necessary to start from other clinical features and laboratory data, independent of nucleic acid detection and chest CT, to provide a basis for early differential diagnosis.

As children age, their range of activities increases and their contact with the outside world increases. As a viral infection, it is obvious that children are especially susceptible to 2019-nCoV infection. The age distribution of the infected children we observed also conforms to this feature, and most of them are asymptomatic or mildly febrile and or symptoms of ARI.[3,21] However, the changes of chest CT are more typical of viral pneumonia,[16] which is consistent with the results of other relevant reports. Also,from the 2019-nCoV cases with coinfection we excluded, they all had fever and symptoms of ARI, chest CT findings of viral pneumonia were also typical. Therefore, 2019-nCoV with other viral coinfections may be more common in children.[8] Pediatric patients should be alert to the possibility of coinfection if severe symptoms appear.Compared with other non-bacterial pathogens,2019-nCoV has more family cluster infections, which indicates that the virus is more infectious and has the ability of sustained human-to-human transmission. When developing preventive and

control measures for children, disinfecting droplets, hand hygiene and sterilization of household environment may be the top priorities.[22]

Early identification of infections has always been a challenge for pediatricians. For the last two decades, most of studies planned to evaluate the roles of biomarkers in defining the etiology of pediatric CAP have been carried out by using, alone or in combination, WBC count, neutrophil percentage, and serum hs-CRP and PCT concentration.[23-24] Among these traditional biomarkers,hs-CRP and PCT have shown superior value in distinguishing bacterial and viral infections as well as bacterial coinfections. PCT appears to be most effective in selecting bacterial cases and assessing severity. However, the precise cut-offs between the separation of bacteria from viruses and the separation between mild and severe separations have not been established.[25] In adults, most patients with CAP and a PCT concentrations <0.5 ng/mL do not require antibiotic treatment because the disease may be viral and can be resolved spontaneously. Data regarding children, despite being limited, are consistent with those collected in adults. Li Z et al found that serum PCT level could provide a useful method of distinguishing bacterial coinfections from an H1N1 influenza infection alone in children during the early disease phase.[26] Chen ZM et al also suggested using a PCT>0.5 ng/mL to identify 2019-nCoV with bacterial coinfections.[10] However, the role of PCT in identifying between viruses and viruses or viral coinfection in children remain unknown.

Our investigation also used the criterion of PCT>0.5 ng/mL to exclude bacterial infection or coinfection. Three cases in the non-2019-nCoV group considered bacterial infections, and one case in the 2019-nCoV confirmed group had IFN A coinfection, but the possibility of combined bacterial coinfection cannot be ruled out. Interestingly, the PCT of the other three cases with RSV coinfection in the 2019-nCoV confirmed group was still significantly higher than that of 2019-nCoV infection alone.Limited to laboratory testing methods and personnel during the epidemic, except for 2019-nCoV, our hospital can only perform RT-PCR detection of IFN A, B, RSV and cytomegalovirus. Unidentified nonbacterial infections may be other types of viral infections. It also does not rule out that some 2019-nCoV

infections may have these other viruses coinfection.Our single-center retrospective small-sample cohort study also has some limitations.Although the levels of hs-CRP and PCT in the 2019-nCoVcomfirded group were significantly reduced,compared with other non-bacterial infections, whether the hs-CRP and PCT in the true world were reduced, that is,whether they are specific, requires further evidence to support.

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Table 1: Univariate analysis between 2019-nCoV confirmed group and non-2019-nCoV group

Items	2019-nCoV confirmed (n=35)	non-2019-nCoV (n=33)	P	OR	95%CI
Age (years)	7.2 (3.9-11.4)	5 (2.1-7.8)	0.031		
Male gender:n(%)	15 (42.9%)	19 (57.6%)	0.332	0.744	0.46-1.205
Body temperature (□)	36.7 (36.2-36.9)	37 (36.7-37.9)	0.001		
Heart rate (times/min)	97.1±16.8	109.7±15.6	0.002		
Respiratory rate (times/min)	22 (20-22)	22 (20-24)	0.092		
Fever:n(%)	12 (34.3%)	29 (87.9%)	<0.001	0.39	0.242-0.628
Symptoms of ARI:n(%)	13 (37.1%)	27 (81.8%)	<0.001	0.454	0.287-0.719
Asymptom:n(%)	16 (45.7%)	1 (3.0%)	<0.001	15.086	2.117-107.475
CT positive findings:n(%)	25 (71.4%)	13 (39.4%)	0.014	1.813	1.131-2.908
Cluster infection: n(%)	29 (82.9%)	5 (15.2%)	<0.001	5.469	2.405-12.433
WBC (×10^9/L)	5.37 (4.67-8.1)	6.94 (5.72-8.86)	0.198		
N %	39.4±14.9	52.5±17.5	0.001		
L%	45.3(39.2-56.6)	33.2 (22.7-42.5)	0.001		
N count (×10^9/L)	2.25 (1.43-3.53)	3.33(2.8-5.18)	0.007		
L count (×10^9/L)	2.68 (1.99-4.01)	2.26(1.66-2.92)	0.123		
Hb (g/L)	128(124-142)	130.0(119-137)	0.572		
PLT count (×10^9/L)	279.1±77.5	263.4±65.1	0.37		
hs-CRP (mg/L)	5.52 (1.1-9.04)	9.04 (7.35-9.54)	0.002		
PCT (ng/mL)	0.05 (0.03-0.08)	0.1(0.05-0.21)	<0.001		

Supplemental table 1: clinical and laboratory data from excluded cases

	Case1	Case2	Case3	Case4	Case5	Case6	Case7	Case8	Case9
Age (years)	1.8	1.3	3	3.7	5.4	1.8	5.6	0.7	4
Gender:M/F	M	F	M	M	F	F	F	M	M
Temperature (℃)	37.8	39.3	39.1	39.5	37.9	37.8	36.8	36.1	36.8
HR (times/min)	100	120	125	135	119	110	90	122	112
RR(times/min)	20	36	25	26	22	30	20	24	24
Fever:Y/N	N	Y	Y	Y	Y	Y	Y	Y	Y
Symptoms of ARI: Y/N	N	Y	Y	Y	Y	Y	Y	Y	Y
Asymptom: Y/N	Y	N	N	N	N	N	N	N	N
CT positive findings: Y/N	Y	Y	Y	Y	N	Y	N	Y	Y
Cluster infection: Y/N	N	N	N	N	N	N	Y	N	N
WBC (×10^9/L)	10.56	6.99	5.61	4.38	22.67	9.66	5.84	7.85	15.04
N %	52.6	30.2	66.1	58.1	71	27.3	48.8	34.3	34.4
L%	39.3	63.7	26	27.2	19.5	63.3	40.6	54.3	49.9
N count (×10^9/L)	5.56	2.12	3.71	2.55	16.11	2.64	2.85	2.7	5.17
L count (×10^9/L)	4.15	4.45	1.46	1.19	4.42	6.11	2.37	4.26	7.51
Hb (g/L)	125	105	106	129	118	121	116	110	151
PLT (×10^9/L)	383	374	138	116	437	277	178	285	614
hs-CRP (mg/L)	14.2	10.4	63.13	14.1	12.46	5.01	19.6	2.55	28.4
PCT (ng/mL)	0.759	0.131	1.37	0.234	0.908	0.154	2.96	0.134	0.1
Coinfection: Y/N	N	Y	Y	Y	N	Y	Y	Y	Y
Pathogens	unknow	RSV+MP	INF A+ unknow	INF A + MP	unknow	nCoV +RSV	nCoV +INF B	nCoV +RSV	nCoV +RSV