



Effective Treatment and Recovery of SARS-CoV-2 Infected Infant/Children in a Family Cluster Outbreak

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Abstract

Purpose: This study aimed to diagnose coronavirus infection in children based on clinical, laboratory, imaging features and its treatment.

Methods:

Design: Diagnosis and treatment.

Setting: Henan Provincial Children's Hospital, Henan Zhengzhou 450018, China.

Subjects: Five patients including 2 males and 3 females aging between 5 days to 8.6 years.

Intervention: All patients underwent throat swabs and blood nucleic acid tests, chest radiography and Computed Thermography (CT) examinations. The patients were treated with interferon nebulization, oral Chinese medicine, ribavirin and lopinavir/ritonavir orally (1.5 ml, 2 times/d × 5d). Main outcome measure: We considered gender, age, and epidemiology and laboratory examination data.

Results: Patient 1 showed reduction in hemoglobin and erythrocytes with 22 time increased dose of D2-polymer compared with other four patients. The blood cell sedimentation rate in patient 1 was 40 while in others it was normal. The C-reactive protein, calcitonin and influenza-A, B virus were normal, while SARS-CoV-2 nucleic acid by throat swab and blood tests were positive in all patients. Three of the chest radiographs showed rough lung texture, but CT case 1 showed small patchy shadows in multiple sites, cases 2 and 3 showed patchy shadows of the right lung, and cases 4 and 5 were normal. All five patients cured, discharged, and followed up were normal.

Conclusion: Other than critical case, the symptomatic treatment was given with a good prognosis. Attention should be paid to avoid transmission among family members, and timely monitoring and evaluation of the pediatric status of infected families for early detection and diagnosis.

Keywords: Children; Novel coronavirus; Infection; Diagnosis; SARS-CoV-2

Introduction

The data on epidemiological and clinical characteristics in pediatric patients are limited. The cluster infection of COVID-19 in a family of five including 10-year children was reported from Wuhan in late January [1].

Compared to adults, the clinical manifestations and lung CT abnormalities of patchy opacities are more modest in children [2]. In China, as of February 7th, 2020, this new form of COVID-19 pneumonia was reported in 285 children, including 10 newborns [3,4].

The new Coronavirus (SARS-CoV-2) has caused huge losses to human life and the economy. The number of confirmed COVID-19 cases and deaths has been increasing in the many countries of the world, but data on the epidemiological and clinical characteristics of pediatric patients are limited. Children have become susceptible to SARS-CoV-2 infection due to immature immune function. As of 24:00 on February 7th, 2020, 285 children with new-type Coronavirus pneumonia were reported nationwide, including 10 newborns. Epidemiological investigations suggest that the population is generally susceptible to the new Coronavirus, and some children have a clear family

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gathering history [3,4].

National Health Commission of the People's Republic of China, 'Notice on Issuing a COVID-19 Infected Pneumonia Diagnosis and Treatment Plan (Trial Version 7)' on March 3rd, 2020, mentions that children, infants, and neonates are also susceptible to the new Coronavirus. They may present with atypical symptoms of malaise, shortness of breath, and the gastrointestinal manifestation of vomiting and diarrhea. Yet, most of the affected children presented with mild disease with low fever and fatigue without clinical features of pneumonia [5]. In this paper, we aim to share our experience of clinical course and management of COVID-19 in newborn and children treated at the specialized referral children hospital in Henan, China.

Materials and Methods

Subject retrospective case summary

Five children who were diagnosed with SARS-CoV-2 new Coronavirus infection through nucleic acid testing and other treatment in Henan Provincial Children's Hospital (Children's Hospital Affiliated to Zhengzhou University) from January to February 2020 were enrolled as research subjects. Five patients including 2 males and 3 females aging between 5 days to 8.6 years were treated. Among them, one was asymptomatic, three were mild, and one was of critical illness. This study was approved by the Ethics Committee of Zhengzhou Children's Hospital and informed consent was obtained from the children's families.

Methods

1. Diagnostic criteria.

- Both throat swabs and blood nucleic acid tests were positive.
- The diagnostic criteria were conducted following the first edition of the Chinese Journal of Pediatrics "Children's 2019 New Coronavirus Infection Diagnosis and Prevention Suggestions" on a trial basis.

2. According to the ICD-10 number, query and retrieve clinical data through electronic medical records. The gender, age, epidemiology, laboratory examination, and imaging data (chest X-ray and CT) of the children were collected and analyzed.

3. Clinical types according to the infection status of children and the clinical characteristics of a confirmed diagnosis, they are divided into five types [5,6]: Asymptomatic infection, mild, common, severe, critical.

Statistical methods

Descriptive analysis, measurement data are expressed as M (range).

Results

General information

There were five children from four families, 3 girls and 2 boys, age minimum of 5 days (case 1) to a maximum of 8 years and six months (case 5). Case 4 and 5 were siblings both female (Table 1). Epidemiological findings revealed cluster infection in families involving 20 members in total, including grandparents, parents, and sisters of the infected child who presented to the hospital. Fever was seen in four children (except case 3), with a maximum of 38.6°C. None had runny nose, vomiting, or diarrhea. The median hospital stay was 16 days, highest of 29 days (case 1) and lowest 15 days (case 4 and 5) (Table 1). The minimum age is 5 days after birth. The parents lived in Wuhan until the child was born. Department G1P1, born 38+5 weeks after cesarean section, A's score, and other unknown. Before admission, the parents of the child returned to Xinyang, Henan from Wuhan on January 22nd, and the mother of the child felt cold and lethargic in the afternoon. A cesarean section was performed on January 31st, and a new Coronavirus infection was confirmed on February 1st with a positive nucleic acid test, indicating that the mother had a new Coronavirus infection during childbirth.

Although the new coronavirus infection occurred only five days after birth, it suggested that it was not caused by vertical infection of mothers and infants. Because the mother was infected with the new Coronavirus before cesarean section (Table 1).

Clinical manifestations and laboratory tests

Laboratory data are shown in Table 2 and 3, WBC was highest $12.41 \times 10^9/L$ (case 1) and lowest 4.79 (case 2). The lymphocyte percentage was high in case 1 and 2, and low in the other three cases ranging from 24.7% to 31.9%.

Hemoglobin was lowest at 10.1 g/L and red blood cells $3.07 \times 10^{12}/L$ in case 1. Platelet was $>440 \times 10^9/L$ (in two cases: case 2 and 3). Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Lactate Dehydrogenase (LDH), and Creatine Kinase isoenzymes (CK-MB) were normal or not requested in all five cases. The D-dimer (D-2 polymer) was high at 22.48 ug/L in case 1 more than 50 times than others (lowest 0.2 in case 3).

Chest X-ray showed increased lung markings in case 1, 2, and 3. Chest CT showed multiple small patches in both lungs in case 1 (Figure 1). In case 2 and 3, patches were seen in the right lungs on

Table 1: Clinical profile of Children with COVID-19 treated at Henan Children's Hospital, China, during January to March 2020.

| No. | Gender | Age | Adm. | Clinical category | Epidemiology | | | Main Clinical Manifestations | | | | Fever (d) | Hospitalized (d) |
|-----------------|--------|------|------|-------------------|--------------|---------------|-------------------|------------------------------|--------|-------|-------------------|-----------|------------------|
| | | | | | Family +ve | Wuhan related | Exp. to Diag. (d) | Fever (°C) | Sneeze | Cough | Vomiting/diarrhea | | |
| 1 [*] | M | 5D | 2/2 | Critical | 5 | Y | 5 | 38 | N | Y | N | 18 | 29 |
| 2 | F | 6M | 30/1 | Mild | 3 | Y | 4 | 38.1 | N | Y | N | 5 | 16 |
| 3 | M | 7Y6M | 19/2 | Mild | 2 | Y | 20 | Normal | N | N | N | N | 16 |
| 4 ^{**} | F | 6Y7M | 2/2 | Mild | 5 | Y | 8 | 38.6 | N | N | N | 2 | 15 |
| 5 ^{**} | F | 8Y6M | 2/2 | Mild | 5 | Y | 9 | 37.4 | N | N | N | 2 | 15 |

No.: Case Number; Adm: Admission Date; Family +ve: Family Members Tested Positive for COVID-19; Expo to diag: Exposure to Diagnosis Days; Vom/diarr: Vomiting and Diarrhea; Fevr: Fever Persisting for Days; Stay: Hospital Stay in days; Y: Yes; N: no

Case 1: The parents lived in Wuhan, Hubei and returned to Xinyang, Henan on 22 January 2020. Same day in afternoon of returning, mother felt cold and lethargic but took it at exertion from travel. She had cesarean delivery on January 31st, G1P1, 38+5 weeks. She had positive nucleic acid test for COVID-19 on February 1st. ^{**} were siblings

Table 2: Laboratory examination of 5 children COVID-19 treated at Henan Children's Hospital, China, during January to March 2020.

| No. | Blood Tests | | | | | |
|-----|----------------------------|---------|-------|-----------------------------|-----------|----------------------------|
| | WBC (× 10 ⁹ /L) | N (%) | L (%) | RBC (× 10 ¹² /L) | HGB (g/L) | PLT (× 10 ⁹ /L) |
| 1 | 12.95 | 0.00505 | 0.495 | 3.07 | 101 g/L | 356 |
| 2 | 4.79 | 0.00175 | 0.772 | 5.05 | 127 g/L | 451 |
| 3 | 9.02 | 0.00613 | 0.319 | 5.23 | 148 g/L | 447 |
| 4 | 4.82 | 0.00427 | 0.247 | 4.52 | 126 g/L | 283 |
| 5 | 5.02 | 0.00388 | 0.271 | 4.6 | 135 g/L | 261 |

No.: Case Number; WBC: White Blood Cells; L: Lymphocytes; N: Neutrophils; RBC: Red Blood Cells; PLT: Platelets

Table 3: Laboratory examination of 5 children COVID-19 treated at Henan Children's Hospital, China, during January to March 2020.

| No. | CRP (mg/L) | PCT (ng/dL) | ESR (mm/h) | Flu virus A/B | ALT (U/L) | AST (U/L) | LDH (U/L) | CK MB (U/L) | D-2 polymer | Chest radiograph | Chest CT |
|-----|------------|-------------|------------|---------------|-----------|-----------|-----------|-------------|-------------|--------------------|-----------------------------|
| 1 | <0.5 | 0.092 | 40 | NA | 46.7 | 37.8 | NA | 48.3 | 22.48 | Rough lung texture | Multiple small patches |
| 2 | 0.5 | 0.11 | 11 | - | 21.8 | 55.3 | NA | NA | 0.4 | Rough lung texture | Multiple small patches |
| 3 | <0.5 | 0.039 | 12 | - | 48.4 | 32.8 | 261.3 | 14.7 | 0.2 | Rough lung texture | Patchy shadow of right lung |
| 4 | NA | NA | NA | NA | NA | NA | NA | NA | NA | Normal | Normal |
| 5 | NA | NA | NA | NA | NA | NA | NA | NA | NA | Normal | Normal |

No.: Case Number; CRP: C-Reactive Protein; PCT: Procalcitonin; ESR: Erythrocyte Sedimentation Rate; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; LDH: Lactate Dehydrogenase; CK-MB: Creatine Kinase-Myocardial Band; D-2: D-dimer (D-2 polymer); NA: Not applicable

Table 4: Imaging (chest X-ray, chest CT) of 5 children with COVID-19 treated at Henan Children's Hospital, China, during January to March 2020.

| No. | Sex | Age | Chest X-ray increased lung marking | Chest CT multiple small patches |
|-----|-----|------|------------------------------------|---------------------------------|
| 1 | M | 5d | Y | Y both lungs |
| 2 | F | 6m | Y | Y right lung |
| 3 | M | 7y6m | Y | Y right lung |
| 4 | F | 6y7m | Normal | Normal |
| 5 | F | 8y6m | Normal | Normal |

No.: Case number; M: Male, F: Female; Y: Yes; * were sibling

Table 5: Treatment of 5 children with COVID-19 treated at Henan Children's Hospital, China, during January to March 2020.

| No. | Heart failure | ICU | Mechanical ventilation | Supportive oxygen therapy | Nebulized inhaled interferon alpha-2b | Ribavirin | Lopinavir/ritonavir | Oseltamivir | Cefoperazone | Glucocorticoid | Immunoglobulin (IVIG) | Chinese herbal medicine |
|-----|---------------|-----|------------------------|---------------------------|---------------------------------------|-----------|---------------------|-------------|--------------|----------------|-----------------------|-------------------------|
| 1 | N | Y | Y | Y | Y | Y | Y | N | Y | N | Y | Y |
| 2 | N | N | N | N | Y | N | Y | N | N | N | Y | Y |
| 3 | N | N | N | N | Y | Y | N | N | N | N | N | Y |
| 4 | N | N | N | N | Y | Y | N | N | N | N | N | Y |
| 5 | N | N | N | N | Y | Y | N | N | N | N | N | Y |

No.: Case Number; ICU: Intensive Care Unit; Y: Yes; N: No

Table 6: The nucleic acid test of 5 children with COVID-19 treated at Henan Children's Hospital, China, during January to March 2020.

| No. | Test, result | Test, result | Test, result | Test, result |
|-----|--------------|--------------------|--------------------|---------------------|
| 1 | Feb 4, TS + | Feb 29, TS -, BI - | | |
| 2 | Feb 1, TS + | Feb 6, TS + | Feb 11, TS -, BI - | Feb 12, TS -, BI - |
| 3 | Feb 15, TS + | Feb 19, TS + | Feb 29, TS - | |
| 4 | Feb 2, TS + | Feb 3, TS + | Feb 10, TS -, BI - | Feb 11 TS -ve, BI - |
| 5 | Feb 3 TS + | Feb 10 TS -, BI - | Feb 11 TS -, BI - | |

No.: Case Number; TS: Throat Swab; BI: Blood nucleic acid test

chest CT. The siblings, case 4 and 5 had normal CT and chest X-ray findings (Table 4).

Treatment

The treatment, heart failure was seen in the 5-day age neonate, case 1, requiring ICU care with mechanical ventilation and immunoglobulin. Remaining 4 cases were mild and managed in a

high dependency unit without ICU or ventilation. Supportive care with nebulization containing interferon α-2b was given to all five children. Oral Chinese medicine was used in all. Ribavirin was used in four children. Case 1 and 2 received lopinavir/ritonavir oral 1.5 ml, 2 times/d for 5d. Glucocorticoid and oseltamivir were not used in any children (Table 5).

The outcome was the full recovery in all five children. Before discharge, all tested negative for the COVID-19 nucleic acid test (Table 6). The family was advised to continue to separate the child and observe at home for two weeks after the discharge. At two weeks regular follow all were doing well.

Discussion

Familial cluster infection 5 children from four family epidemiology suggest a family cluster infection, of which 20 family members were involved in the infection. Including grandparents, grandma, father, mother, and sister. Among them, the neonates were critically ill only 5 days after birth. Before birth, his parents were in Wuhan. After the mother became infected with the new coronavirus pneumonia, she had a fever and then had a cesarean section. A positive checkup confirmed the diagnosis.

Clinically, fever is the main manifestation. Four children (80%) had a fever ranging from cough, asthma, vomiting, and diarrhea. This shows that fever is the most common manifestation of neonatal coronavirus infection in children. It's also a signal and a clue. It is the first performance that should be taken seriously. Italian studies report that fever is the most common manifestation of 83% to 98%, while cough and shortness of breath account for 31% to 55%. None of the 5 children had congenital, genetic, and metabolic diseases [6-9].

According to its symptoms and clinical manifestations, it is divided into an asymptomatic infection, mild, common, severe, and critical. Studies suggest that children with a new type of coronavirus infection have five clinical characteristics. First, the number of infections is smaller than that of adults. Second, symptoms and clinical manifestations are lighter than those of adults. Third, there are fewer complications than adults. Fourth, recoveries are faster than that of adults, and fifth have a better prognosis. This may be related to less exposure of children than adults, pediatric immune function is not yet fully developed, pediatric infections are mild and inaccurate, and therefore, the diagnosis cannot be found in time and is easily missed.

Five cases had family members with a history of infection. Fever is the main symptom of most children. Except for Example 3, fever is low to moderate, with a maximum body temperature of 38.6°F. The clinical and immunological characteristics of children need attention, and further research and discussion are needed. One patient in this group had no clinical manifestations despite a nucleic acid test and a family member who was diagnosed with a new coronavirus infection. It should be noted that children with asymptomatic infection should be vigilant because those with no symptoms or mild symptoms are likely to become a hidden source of infection that should be paid attention to. It has been reported that most of the early lymphocytes were reduced in adults and lower in 4 cases. Leukocytes in children under 5 years of age have two crosses. Lymphocytes are normally higher than neutrophils. So if the lymphocytes decrease, it may be related to viral infection.

Increased D-dimer is an indicator of serious infection. The D-dimer in this group of cases was as high as 22.248. It was 22 times higher than in other cases, but there was no significant difference between C-Reactive Protein (CRP), Procalcitonin (PCT) in mild and critical illness. In adult patients, AST, ALT, LDH, isoenzymes, etc. increased, but no significant increase in children in this group. A positive nucleic acid test is an important basis for the diagnosis of new crown infection. In this group of 5 children, throat swabs, blood

nucleic acid tests were positive twice, and no negative children. The patient was discharged from the hospital with a negative secondary test and continued to be separated and observed at home for two weeks after discharge [3,7].

It has been reported that the nucleic acid test may be negative in the early stage, so the chest radiograph and CT of epidemiological history and symptoms suggest that children with new crowns should be repeatedly tested for nucleic acid to avoid missed diagnosis. Negative throat swabs but positive anal swabs have been reported to indicate a long period of exclusion of the virus from the intestinal tract. Chest radiographs of 3 patients in this group showed rough lung texture, but CT examination showed patchy consolidation shadows in multiple parts of both lungs and right lung.

It shows that chest CT is earlier and more diagnostic value than chest radiograph. Given the low sensitivity of nucleic acid detection, to prevent missed diagnosis, epidemiological and clinical manifestations should be combined, and combined diagnosis of nucleic acid examination and chest CT should be used to reduce missed diagnosis [8].

In terms of treatment: Because children with neo-crown infections are less ill and have a better prognosis, they are mainly family-gathered. For ordinary, asymptomatic, mild cases, a special medication is not emphasized. Except for case 1 who was treated in the ICU in the group, the remaining 4 cases were closely observed after hospitalization, and they were cured after being supported by symptomatic treatment. No special changes were observed after two weeks of follow-up. Example 1, the patient recovered and was discharged from the hospital despite the onset of disease on 5 days after birth and treatment with mechanical ventilation. The application of antiviral drugs such as ribavirin in children with new crown infection suggests that further studies on efficacy, safety, and toxic side effects are needed. Patients 1 and 2 orally took lopinavir/ritonavir orally (1.5 ml, 2 times/d × 5d) antiviral treatment. None of the 5 patients received oseltamivir phosphate [4,6,8,10,11].

Except for neonates in this group, the remaining four cases were not treated with antibiotics, and emphasis was placed on avoiding blind or incorrect use of antibacterial drugs. Reasonable selection of antibiotics should be based on bacterial infection and bacterial culture and drug sensitivity tests. For critically ill patients, a short course of small doses of gamma ball and glucocorticoid can be given. The application of traditional Chinese medicine should be treated with individualized syndromes according to the age, physique, and condition of the child. It is recommended to take traditional Chinese medicine instead of injecting traditional Chinese medicine preparations.

α-2b interferon nebulization, as a medication for respiratory diseases, is currently widely used, but the clinical efficacy of novel coronavirus infection is still lacking theoretical and clinical evidence of rigorous scientific research such as randomized double-blind placebo control. Therefore, further clinical rigorous scientific research is needed to provide scientific theoretical and experimental evidence for clinical applications. Moreover, atomization may increase the risk of aerosol infection, which deserves further discussion and discussion.

Conclusion

Other than critical case, the symptomatic treatment was given with a good prognosis. Attention should be paid to avoid transmission

among family members, and timely monitoring and evaluation of the pediatric status of infected families for early detection and diagnosis.

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