Clinical Analysis of 9 Cases of Neonatal Influenza A

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Research

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Abstract

Background: The population is generally susceptible to influenza A, while neonatal cases are relatively rare. The study aims to explore the clinical characteristics, diagnosis, treatment, and prognosis of neonates with influenza A.

Methods: The clinical data from neonates with influenza A who were treated in the neonatal department of Beijing Ditan Hospital affiliated with Capital Medical University from November 2017 to January 2019 were retrospectively analyzed.

Results: A total of 9 neonates with influenza A were admitted and treated, with a distribution of 7 males and 2 females. The onset was 1.44 ± 1.46 days (mean ± SD), and age at diagnosis was 21.44 ±6. 53 days. All cases had a history of exposure to febrile patients, The main symptoms are fever, nasal congestion, runny nose, sneezing, coughing, other respiratory symptoms and digestive symptoms such as vomiting milk, choking milk, less milk, diarrhea. Laboratory tests showed 7 cases of decreased white blood cell counts, 3 cases of increased plasma C-reactive protein concentrations. All cases were administered antiviral therapy on the day of admission. Eight neonates reverted to a normal temperature within 48 hours after hospitalization, one neonate's temperature returned to normal after 48 hours of hospitalization, and all cases' symptoms gradually improved.

Conclusion: The symptoms of influenza A in neonates are atypical, once a diagnosis is confirmed, the prognosis is likely to be favorable as long as antiviral treatment with antiviral is initiated as soon as possible.

1 Background

Influenza viruses are divided into types A, B, and C. The principal cause of influenza pandemics is type A, while a few pandemics are type B; and type C only causes insignificant or mild upper respiratory tract infections. In the influenza season, more than 40% of preschool children and 30% of school-age children contract influenza [1]. Symptoms such as laryngitis, tracheitis, bronchitis, bronchiolitis, pneumonia, and gastrointestinal symptoms caused by influenza A virus are also more common in children than in adults [2]. Children and immunocompromised influenza A patients often experience complications and may even die. Infants and neonates are at high risk of influenza A due to their relatively weaker immune function and tendency to develop serious complications such as pneumonia, and this predicts a poor prognosis [3]. As a special population, neonates may exhibit different routes of infection, clinical manifestations, treatment options, and outcomes of influenza virus infection relative to children of other ages. At present, there are few studies that focus on neonatal influenza A virus infection in China or internationally. Therefore, we retrospectively analyzed the clinical data from 9 neonates diagnosed with influenza A who were admitted and treated at our hospital over the past 2 years, and also analyzed and summarized their clinical characteristics in order to improve clinical diagnosis and treatment of neonatal influenza.

The study was approved by the Ethics Committee of Beijing Ditan Hospital affiliated to Capital Medical University.

2 Subjects And Methods

2.1 Research subjects

Neonates with a diagnosis of influenza A infection who were admitted to the pediatric department of our hospital from November 2017 to January 2019 were selected as research subjects.

Inclusion criteria were (1) age in days at diagnosis ≤ 28 d; (2) a recent contact history of fever patients; (3) having 1 of the following clinical manifestations—fever, stuffy nose, runny nose, coughing, sneezing, choking on milk, spitting up milk, poor appetite, and diarrhea; and (4) a nasal/pharyngeal swab screening test that was positive for influenza A virus antigen.

Exclusion criteria were individuals with nasal/pharyngeal swab screening who tested positive for influenza A virus antigen, but showed no obvious influenza-like symptoms; and no recent history of exposure to febrile patients.

Diagnosis of Influenza A [4]. **A.** Clinical diagnosis: the above-mentioned clinical manifestations of influenza occurred in the case, and there was epidemiologic evidence or a positive rapid influenza antigen test, and other diseases causing influenza-like symptoms were excluded. **B.** Confirmed diagnosis: the neonate exhibited the above clinical manifestations of influenza, and demonstrated positive results with 1 or more of the following pathogenic tests—(1) positive detection of influenza virus nucleic acid, (2) positive isolation and culture of influenza virus, and (3) levels of influenza virus-specific IgG antibody in both sera of the acute and recovery phases that increased 4-fold or more.

Diagnosis of severe Influenza A: Severe cases were confirmed when 1 of the following conditions occurred: (1) persistent high fever > 3 d in duration, accompanied by severe cough, purulent sputum, blood sputum, or chest pain; (2) rapid breathing rate, difficulty breathing, lip cyanosis; (3) slow response, drowsiness, restlessness, convulsions; (4) severe vomiting, diarrhea, dehydration; (5) combined pneumonia; and (6) the original underlying disease significantly worsened.

2.2 Methods

2.2.1 Data collection: We collected general information of neonates, including gender, gestational age, birth weight, time of onset, age in days at diagnosis, duration of fever, length of hospital stay, clinical manifestations, physical signs, laboratory test results, treatment, and prognosis.

2.2.2 Laboratory detection method for influenza A virus: nasal/pharyngeal swab specimens were collected from all cases on the day of admission. The insertion depth of the swab was approximately the linear distance from the nostril to the ear lobe. The specimens were collected and placed in sealed plastic tubes with screw caps, and sent to the Department of Laboratory Medicine, Beijing Ditan Hospital, Capital Medical University for testing. An immunofluorescence method was used to detect influenza virus antigen, and real-time RT-PCR was used to detect influenza A virus nucleic acid.

2.2.3 Statistical Analysis: Measurement data that conformed to a normal distribution are described as means ± standard deviation ($\bar{x} \pm s$), and measurement data that were not normally distributed are described as medians. Descriptive statistics are expressed by a proportion (%).

3 Results

3.1 General information

A total of 9 neonates with influenza A were diagnosed, with all of them term infants— including 7 males and 2 females. There were 6 cases of natural delivery and 3 cases of cesarean delivery. The mean gestational age was 39.0 ± 0.86 weeks, and mean birth weight was 3577.44 ± 330.72 g. The age at onset was 3–28 days, and the median age was 22 days. All neonates had a history of contact with febrile patients, including 2 cases of fever in the mother and 7 cases of fever in other relatives. The mean age at diagnosis was 21.44 ± 6.53 days. None of the mothers of the 9 neonates were vaccinated against influenza during their pregnancies. The length of hospital stay was 4–8 days, with a mean of 5.1 ± 1.5 days.

3.2 Clinical manifestations

Fever occurred in 7 of the 9 neonates, with a maximally attained body temperature of 39.5°C and a duration of 1–6 days, with an average of 2.4 ± 1.7 days. There were 6 cases of respiratory symptoms, including 4 cases of nasal congestion, 3 cases of coughing, and 3 cases of runny nose and sneezing. There were 5 cases of digestive system symptoms, including 3 cases of reduced milk intake, 2 cases of spitting up and choking on milk, and 1 case of diarrhea. The physical signs included 8 cases of pharyngeal congestion, 2 cases of coarse breath sounds and audible coarse rales, and 1 case of mottled skin.

3.3 Laboratory tests after admission

Two of the 9 neonates had normal white blood cell (WBC) counts (22.2%), 7 cases had decreased WBC counts (77.8%), 3 cases exhibited increased CRP (33.3%), and myocardial enzymes were augmented in 1 case (11.1%). Liver enzymes, however, were normal. Eight cases showed a positive influenza A nucleic acid test, of which 5 cases were positive for HIN1 nucleic acid, 3 cases were positive for universal nucleic acid test (see Table 1). Five neonates underwent chest radiography and 2 neonates showed complications of pneumonia; and 6 of the 9 neonates underwent ECG examinations, with no obvious abnormalities.

3.4 Severe cases

A total of 3 neonates were diagnosed as severe cases. One neonate had a fever lasting > 3 days with pneumonia, 1 neonate had pneumonia, 1 neonate exhibited elevated myocardial enzymes, and 2 neonates manifested pneumonia without serious complications such as respiratory failure, pleural effusion, pneumothorax and atelectasis; there were no deaths.

3.5 Treatment and prognosis

The 9 neonates were treated with antiviral drugs on the day of admission (paramivir for 2–5 days, which was discontinued after body temperature improved; or oseltamivir for 5 days), and no steroids were administered.Among them, 8 neonates reverted to a normal temperature within 48 hours, and clinical symptoms improved (1 neonate was treated with gamma globulin for recurrent high fever).The other neonate manifested fever for 5 days at the time of admission, complicated by bacterial infection.His symptoms gradually improved after the application of paramivir, cefmetazole, and gamma globulin, and his body temperature returned to normal 6 days after admission. A follow-up chest X-ray showed resolution of inflammation in the lungs. None

of the 9 neonates showed any adverse drug reactions or serious complications, and all of them had a favorable prognosis.

4 Discussion

The general population is susceptible to influenza virus transmission via droplets, aerosols, and direct or indirect contact. Typical clinical manifestations are systemic symptoms such as sudden chills, high fever, headache, general soreness, and weakness; while the respiratory symptoms are mild [6]. In our study, the age at onset for neonates with influenza A was 3–28 days. After birth, these neonates had an obvious history of contact with febrile patients (mother or other family members), and all of them developed symptoms during the influenza incubation period—which is consistent with the typical course of influenza A. The principal source of infection for neonates with influenza A is their caregivers, although the neonates have atypical symptoms due to their low immunity. In addition to fever, nasal congestion, runny nose, sneezing and coughing in neonates with influenza A in our study, digestive symptoms such as spitting up and choking on milk, anorexia, and diarrhea are also relatively common—which is consistent with previous reports [7–8]. Neonates with influenza A may have reduced white blood cell and neutrophil counts, and slightly increased C-reactive protein; but whether antibiotic treatment is needed depends upon the comprehensive assessment of neonatal symptoms, physical signs, and laboratory tests so as to avoid antibiotic abuse.

In the present study, all cases were positive for influenza A virus antigen, and the positivity rate for nucleic acid testing for influenza A virus was 88.9%. One of the cases was negative for nucleic acid testing, but we could not exclude a false-negative due to the collection site of the specimen being unsatisfactory. However, in combination with typical fever symptoms and contact history with febrile patients, all 9 neonates met the clinical diagnostic criteria for influenza A; and 8 neonates met the defined diagnostic criteria for influenza A.

Prompt diagnosis and early antiviral treatment are the most important strategies for treating influenza. Antiviral treatment is best for neonates within 48 hours of symptoms, but for neonates with severe illness or a high risk of complications, antiviral treatment should still be considered 48 hours after symptoms appear [9]. One neonate in the present study was started on antiviral therapy 5 days after the onset of the disease, and the prognosis was still favorable despite the long treatment time. At present, oral oseltamivir is still the first choice for treating childhood influenza; but paramivir can also be a treatment of choice for neonates at certain dosages (see Table 2 for specific dosages). Therefore, early detection, early diagnosis, and early treatment are the primary means to be used to reduce the mortality and serious complications of neonatal influenza [10].

Influenza virus infection during pregnancy can increase the risks of spontaneous abortion, premature delivery, stillbirth, and low birth weight [11–12]. Pregnant women, especially after infection in the third trimester, can also easily develop critical illnesses that can result in death [13]. Influenza vaccination of pregnant women not only effectively prevents maternal influenza during the influenza season, but also produces protective antibodies that can pass through the placental barrier; and thus effectively prevents infection in infants under 6 months of age who are not suitable for influenza vaccination [14–15]. In developed countries such as the United States, the influenza vaccination rate for pregnant women has approached or exceeded 50% [16–17], while the influenza vaccination rate of pregnant women in China has been very low [18]. The latest guidelines suggest [19] that pregnant women be vaccinated at any stage of pregnancy, and that the prevention of contracting influenza by

infants under 6 months of age occur through the vaccination of their mothers during pregnancy, and also of their family members and caregivers.

In summary, the symptoms of neonatal influenza A are often atypical. In addition to fever, nasal congestion, runny nose, sneezing, coughing, and other respiratory symptoms; digestive symptoms such as spitting up milk, choking on milk, reduced milk intake, and diarrhea are also relatively common. Early diagnosis and antiviral treatment can effectively improve clinical symptoms and reduce complications, and paramivir is relatively safe for neonatal use.

Declarations

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CONFLICTS OF INTREST:

All authors declare that they have no conflicts of interest.

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Tables

Table 1.

Laboratory examination of 9 neonates after admission.

No	WBC ($\times 10^9$/L)	N# ($\times 10^9$/L)	N% (%)	L% (%)	CRP (mg/L)	PCT (ng/ml)	CK-MB (IU/L)	AST (U/L)	ALT (U/L)	Influenza A nucleic acid
1	11.87	6.85	57.84	29.34	7.9	0.68	31.1	33.2	9.3	-
2	5.39	0.89	16.62	66.21	8.2	0.07	27.7	21.6	12.4	Universal +
3	7.4	4.47	60.3	13.02	2.8	0.27	980	66.8	11.5	H1N1 +
4	10.56	6.63	62.84	19.02	2.6	0.15	36.3	28.1	16.5	H1N1+
5	5.94	1.92	23.4	67	0.1	0.07	37.9	37.4	15.4	H1N1+
6	5.81	0.72	12.4	76.6	0.3	0.08	31.8	37.6	27.3	Universal +
7	6	1.82	15	69.9	0.8	0.18	29.3	36.2	19.1	H1N1+
8	4.88	1.66	53.5	23	<8	0.26	22.2	37.6	34.9	H1N1+
9	6.11	0.46	9.44	69.6	15.2	0.15	24.5	38.9	17.6	Universal +

Table 2.

The dosage and course of oseltamivir and paramivir in neonates.

Medicine	Therapeutic dose	Prophylactic dose
Oseltamivir		
0–8 m	3 mg/kg, bid; treatment course 5 d	0–3 months of age is not recommended, except in emergencies, and must be applied after clinical evaluation; 3–8 months of age, 3 mg/kg, qd, treatment course 10 d
Paramivir		
< 30 d	6 mg/kg, qd, treatment course 1–5 d	
31–90 d	8 mg/kg, qd, treatment course 1–5 d	
91 d–17 yrs	10 mg/kg, qd, treatment course 1–5 d	