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The first case of Kawasaki disease in a 20-month old baby following immunization with rotavirus vaccine and hepatitis A vaccine in China: A case report

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Abbreviations: LLR, Lanzhou lamb rotavirus; K_D, Kawasaki disease; HAV, hepatitis A virus; WBC, white blood cell; HGB, hemoglobin; PLT, platelet; CRP, C-reactive protein; CK, Creatine kinase; LDH, lactate dehydrogenase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; LMCA, Left main coronary artery; RCA, Right coronary artery; PCT, procalcitonin; HCV-Ab, Hepatitis C virus antibody; TP-Ab, Treponema pallidum antibody; HIV-Ab, Human immunodeficiency virus antibody; IVIG, Intravenous immunoglobulin; FDA, The US Food and Drug Administration; VAERS, Vaccine Adverse Event Reporting System; REST, Rotavirus Efficacy and Safety Trial

Kawasaki disease (K_D) after rotavirus and hepatitis A vaccination has not previously been reported in a baby in China. Herein, we describe a 20-month-old child who developed Kawasaki disease after receiving her second dose of Lanzhou lamb rotavirus vaccine (LLR) and her first dose of freeze-dried live attenuated hepatitis A vaccine. The case report was conducted by collecting and analyzing the hospital in-patient medical records and reviewing both the domestic and foreign pertinent literature. These findings will be important to note this possible side effect and to further investigate the association between the above 2 vaccines and Kawasaki disease.

Introduction

Kawasaki disease (K_D) is an acute, self-limited vasculitis that primarily affects the coronary arteries and occurs predominantly in children under 5 y of age.[1-3] The disease manifests through a variety of signs and symptoms.[4] Epidemiologic studies reveal that it occurs worldwide in individuals of all races, with the highest incidence rates in Japan and in persons of Asian ethnicity.[5-8]

Several vaccines have been involved into the post-vaccination K_D, as for hepatitis B, rabies, measles, and rotavirus vaccine, but K_D after the concomitant administration of hepatitis A vaccine and rotavirus vaccine has not previously been reported in a baby in China.

Rotavirus is the leading cause of severe diarrhea in infants and children worldwide, particularly in developing countries.[9-11] Each year in China, approximately 40,000 rotavirus-related deaths occur.[12] Although rotavirus-associated diarrhea in China, especially in the countryside, is serious and the vaccine is necessary, the rotavirus vaccine is not yet included in the national immunisation plan. Only the Lanzhou lamb rotavirus (LLR) vaccine (Lanzhou Institute of Biological Products, Lanzhou, China) has been licensed for diarrhea prevention in China.[13] More than 30 million doses have been administered to children under the age of 5.[14]

Hepatitis A is an infectious disease of the digestive tract that is caused by the hepatitis A virus (HAV),[15] with a high incidence in China.[16] Hepatitis A vaccines are now widely used worldwide and are routine childhood vaccinations in China. Furthermore, increasing the vaccination rate is the most economic and effective method to control hepatitis A prevalence.[17]

Herein, we describe a case of K_D in a 20-month-old child who developed the disease after receiving her second dose of LLR and her first dose of freeze-dried live attenuated hepatitis A vaccine.

Case Report

A previously healthy 20-month-old female from central southern China was born on October 10, 2012 by Caesarean birth, was breast fed, and had a birth weight of 3.3 kg. The vaccinations the child has had include one dose of Bacillus Calmette Guerin vaccine (BCG), Japanese Encephalitis At-tenuated Live

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Vaccine(JEV), Lantigen B vaccine, Varicella vaccine and LLR; 2 doses of Measles vaccine, Meningitis A vaccine group and Influenza vaccine; 3 doses of Hepatitis B vaccine(HBV), Inactivated Poliovirus Vaccine(IPV) and Haemophilus influenzae type b vaccine(HIB); 4 doses of Acellular pertussis diphtheria tetanus vaccine(APDT). The detailed data was shown in **Table 1**. There was neither a history of any abnormal reaction to preventative vaccination nor any allergies. The child had received her second dose of LLR(3ml; Lanzhou Institute of Biological Products, Lanzhou, China; Vaccine lot number:201308084) vaccination orally and first dose of HAV(0.5ml; PuKang Biotechnology Co., Ltd. Zhejiang, China; Vaccine lot number:201309253)vaccination by injection at 3 p.m. on June 6, 2014, and the above 2 types of vaccines were being administered concomitant. She then developed symptoms of fever and runny nose, which began the night of the vaccination. The pre-examination showed no contraindication to the inoculation.

The child was admitted due to fever and runny nose that began at 8 o'clock in the evening following the vaccination. The hospital diagnosis was a cold, and she was discharged after treatment. She began treatment for acute tonsillitis detoxification on the next day. Five days after the therapy, the patient had not shown improvement.

The patient was admitted to the Country People's Hospital again on June 12 for a persistent 5-day fever with rash and itching. Her temperature was 37.2°C, the heart rate was 186 beats/min and the breathing rate was 32/min. Physical examination revealed many rashes, superficial lymph nodes, conjunctival and pharyngeal congestion, chapped lips, strawberry tongue, antiadoncus, and chest auscultation with rough breath sounds. An initial laboratory investigation revealed a white blood cell (WBC) count of 2.7×10^9/L (normal range 8–10 $\times$ 10^9/L), hemoglobin (HGB) at 118g/L(normal range 100–150g/L), a platelet (PLT) count of 210 $\times$ 10^9/L(normal range 100–300 $\times$ 10^9/L), and C-reactive protein (CRP) at 128.8 mg/L (normal range 0.0–8.2 mg/L). Creatine kinase (CK) was at 56U/L (normal range 26–140U/L), and lactate dehydrogenase (LDH) was at 327U/L(normal range 125–220U/L). A liver function check revealed Alanine aminotransferase (ALT) 119 U/L (normal range 5–40 U/L) and Aspartate aminotransferase (AST) 76 U/L (normal range 8–40 U/L). Chest and abdomen radiographs were normal. Echocardiography revealed tachycardia, and mild dilatation of coronary arteries were found according to the diagnostic criteria,[18] with the diametersof the left main coronary artery(LMCA) and the right coronary artery(RCA) approximately 2.3 mm and 2.2 mm respectively. On the second day of hospitalisation, repeat blood tests revealed a white blood cell (WBC) count of 7.5×10^9/L and procalcitonin (PCT) at 20.31 ng/ml (normal range 0–0.05 ng/ml), which revealed a serious bacterial infection. Serology tests for HCV-Ab, TP-Ab and HIV-Ab were negative.

Based on the clinical findings, the diagnoses of K_D and sepsis were made after expert consultations. Intravenous immunoglobulin (IVIG), aspirin and dipyridamole were administered for treatment, and prophylactic treatment for infection consisting of imipenem-cilastatin sodium and reduning injection was initiated. The child was discharged after recovery on June 26, 2014.

The patient was admitted to a first-class ternary hospital to be checked on August 10. Blood tests revealed a WBC count of 9.82×10^9/L, HGB 136g/L, a PLT count of 343 $\times$ 10^9/L (normal range 100–300 $\times$ 10^9/L); liver function check revealed ALT 9 U/L and AST 33U/L. On the second day of hospitalisation, echocardiography demonstrated that the left and right coronary artery diameters were 2.1 mm and 0.93 mm, respectively, Which showed no abnormality according to the diagnostic criteria.[18] The diagnoses in these 2 hospitals were the same and confirmed by expert consultations.

Discussion

We report a case of K_D in a 2-year-old child who exhibited a strong response that was temporally associated with a second dose of LLR vaccination and a first dose of HAV vaccination. The diagnosis was based on the presence of prolonged fever, rash, conjunctival and pharyngeal congestion, chapped lips, strawberry tongue, and increased levels of acute-phase reactants. According to the results of Echocardiography, coronary artery lesions (CAL) caused by K_D was seen. Then, the patient received IVIG therapy and recovered. This case has not previously been reported in a baby in China and triggered a legal dispute between the patient and the Huarong County Center for Disease Control and Prevention, which led to the timely organization of expert

Table 1. Vaccinations history of the child

Types of vaccines	Vaccination time	Vaccination doses
HBV	2012-10-11/ 2012-11-12/ 2013-04-19	3 doses
BCG	2012-10-11	1 dose
IPV	2012-12-12/ 2013-01-11/ 2013-02-16	3 doses
APDT	2013-01-11/ 2013-02-16/ 2013-04-05/2014-04-16	4 doses
HIB	2013-03-10/ 2013-05-21/ 2013-07-20	3 doses
Lantigen B vaccine	2013-04-05	1 doses
Meningitis A vaccine group	2013-04-19/ 2013-08-18	2 doses
Measles vaccine	2013-06-11/ 2014-04.16	2 doses
JEV	2013-07-20	1 dose
LLR	2013.08.18	1 dose
Influenza vaccine	2013-10-09	2 doses
Varicella vaccine	2013-11-07	1 dose

consultations and to the provincial authorities and relevant departments being assigned to the case. Our work was part of a team of experts who were legally retained to make an evaluation.

Early diagnosis K_D is difficult due to a lack of unique symptoms upon disease onset, and fever is usually the most consistent manifestation.[19] In our patient, fever and runny nose developed early, and only on day 5 did the other clinical symptom of K_D appear. Tachycardia was present on day 5. The clinical characteristics of K_D did not appear until 5 d after the onset of illness when the patient was admitted, which led to a delay in diagnosis and treatment. In addition, children who do not meet the diagnostic criteria may have an incomplete or atypical form of K_D,[19] which is not conducive to the timely diagnosis and treatment of K_D. Thus, based on the hospital in-patient medical records and the process of diagnosis and treatment, it is clear that there are still many insufficiencies and limitations in some grassroots medical organisations in China, such as difficulty in making an early diagnosis and lack of corresponding specific inspection methods.

Hepatitis A vaccination is now used worldwide to treat millions of patients. Niu et al[20] reported that a total of 428 cases had been reported to the US Food and Drug Administration (FDA) hepatitis A Vaccine Adverse Event Reporting System (VAERS) from February 1995 to June 1997, which included 3 cases of vasculitis and 2 cases of purpura. In China, there are also many reports describing the association of hepatitis A vaccine and vasculitis,[21-24] with most of them being purpura.[16] K_D after hepatitis A vaccination has not yet been reported in China or abroad.

Although the LLR vaccine has been licensed for use in China for more than 10 years, few reports on the vaccine's protective effect and safety have been published.[14] The occurrence of K_D that is temporally associated with vaccination has been reported, but a causal relationship has not been established.[3] The result of a phase 3 clinical trial for RotaTeq® (Merck & Co. Inc., Whitehouse Station, NJ, USA), an oral rotavirus vaccine, revealed that the K_D rates are higher, although not statistically significantly, among the rotavirus-vaccinated group compared with placebo recipients.[3,25] FDA approved a revised RotaTeq® label to include the information regarding K_D cases that were identified in this phase 3 clinical trial and reported to the VAERS.[3,25] In addition, the results of a post-marketing surveillance study[26] from the US have not identified any concerns, such as an increased risk of intussusception and Kawasaki disease, related to vaccine safety.[27] In another study, Abrams et al[1] found no evidence of an increased risk of K_D after vaccination. Unexpectedly, vaccination was related to a transient drop in K_D incidence. The Observed potential short-term protective effect of vaccination on K_D is intriguing.

The child developed K_D after receiving the above-mentioned 2 types of vaccinations. In the US, the results from the Rotavirus Efficacy and Safety Trial (REST) showed that RotaTeq® may be administered simultaneously with various other routine vaccines.[28] The concomitant administration of hepatitis A vaccine and rotavirus vaccine did not affect the respective immunogenicities of each agent. However, whether vaccines administered simultaneously may increase the risk of K_D remains unclear and must be researched further. We still suggest staggering these vaccinations. Whether the stability of the vaccine in the process of cold chain and transport play some role in an increased risk of K_D also remains to be researched further.

The pathogenic mechanism of K_D in this baby is not clear, but it is possible that vaccination played some role in the pathogenesis of K_D.[29,30] Here, we have not identified any concerns related to the vaccination, such as Kawasaki disease, and the association in this child may be coincidental. Although it is impossible to establish a causative effect based on an individual case report, this case still should be reported, and sufficient attention should be paid to it in China, which is the world's largest developing country and the largest market for this vaccine. It could alert us to the possibility that the onset of K_D may be a rare and severe side effect of rotavirus vaccination. Ongoing epidemiological research and further monitoring could help to answer this question.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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