



## Case report

# Differential congenital cytomegalovirus infection in dichorionic diamniotic twins—A case report and literature review



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## ABSTRACT

**Background:** Cases of differential congenital cytomegalovirus (CMV) infection in twins are rarely reported. The chance of congenital infection and the clinical outcome of monochorionic diamniotic or dichorionic diamniotic twins are highly uncertain.

**Cases presentation:** We reported a case of differential congenital CMV infection in dichorionic diamniotic twins. Despite being exposed to the same maternal environment and similar genetic background, twins reacted differently to maternal infection and presented with non-concordant infection status. The potential mechanism of discordant infection from aspects of type of chorion and placenta and immune status has been discussed through literature review.

**Conclusion:** CMV infection can present as differential congenital infection in twin pregnancy, with various clinical symptoms. Fetal cellular immune function may be involved in the pathogenesis.

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## Introduction

CMV is a leading cause of congenital infections worldwide, affecting from 0.3% to 2% of liveborn infants, about 10–15% of newborns show clinical symptoms after birth [1]. However, cases of differential CMV intrauterine or congenital infection in twins are rarely reported. Studies in the past decades have shown that the chance of congenital infection and the clinical outcome of monochorionic diamniotic or dichorionic diamniotic twins were variability [1]. Although the monochorionic diamniotic twins were exposed to the same maternal environment and shared the similar genetic background, occurrence of CMV infection could be presented in only one of the twins. It is uncertain the reason why differential CMV infection status appeared in twins, which leading to many clinical questions: whether the single infection in twins is related to the type of chorion and placenta, whether the virus is fetal-fetal transmission, and whether the immune status of the fetus affecting clinical outcome and prognosis [4]. In this study, we reported a case of differential congenital CMV infection in dichorionic diamniotic twins, and analyze this differential infection through literature review.

## Cases presentation

## General Information

A 33-year-old woman had naturally conceived triplets after taking ovulation drugs. Fetal reduction was performed at 8 week of gestation, 2 fetuses were retained, and amoxicillin was given for 5 days to prevent infection. In routine laboratory screening during the first trimester of pregnancy, absence of cytomegalovirus immunoglobulin M (CMV-IgM) and the presence of cytomegalovirus immunoglobulin G (CMV-IgG) (126 U/ml) were showed in TORCH (Toxoplasma, Rubella virus, Cytomegalovirus, Herpes simplex virus) results. Non-invasive prenatal screening and ultrasound examination indicated a low risk of the twin fetus, and no obvious anomalies were seen in the second trimester. She was healthy during pregnancy until delivery. Cesarean delivery was performed at GA of 34<sup>+5</sup> weeks due to premature rupture of membranes. Dexamethasone was given intramuscularly 12 h before delivery. The placenta was dichorionic-diamniotic, and the twins (the first twin A, the second twin B) were found with umbilical cords around their necks.

## Clinical features, diagnosis and treatment

The twins were male who showed premature appearance, no skin damage, and no specific abnormalities of the head, eyes, nose and ears. The first-born infant (twin A) had a birth weight of 2500 g (percentile

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**Table 1**  
Clinical features and Immunologic tests.

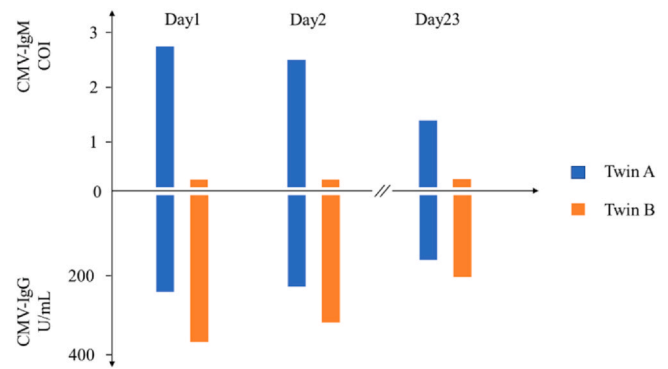
Fetus		Twin A	Twin B	
Gender		Male	Male	
Birth weight(g)		2500	1830	
Apgar scores	1 min	7	8	
	5 min	7	8	
CPAP (days)		3	3	
Antibiotics (days)		Am/FI(3)	Am/FI(3)	
Antiviral therapy		No	No	
Hospital stays (days)		9	11	
Feeding		Formula	Formula	
Cytokines	IFN-gamma (pg/ml)	2.45	2.24	
	IL-10 (pg/ml)	8.41	7.24	
	TNF-alpha (pg/ml)	5.33	4.6	
	IL-4 (pg/ml)	4.16	4.26	
	IL-6 (pg/ml)	63.41	79.8	
	IL-2 (pg/ml)	5.44	5.36	
	Lymphocytes subtypes	CD3%	86.39	86.17
		CD3 (/ul)	2488	2495
CD4%		54.8	63.7	
CD4 (/ul)		1578	1844	
CD8%		31.2	22.7	
CD8 (/ul)		898	656	
CD4/CD8		1.8	2.8	
CD19%		7.5	7.9	
CD19 (/ul)		215	230	
CD16 +CD56%		3.7	4.6	
Immunoglobulin	IgG (g/L)	3.64	4.62	
	IgA (g/L)	0.259	0.259	
	IgM (g/L)	0.181	0.181	
	IgE (kU/L)	17.1	17.1	
	C3 (g/L)	0.53	0.51	
	C4 (g/L)	0.241	0.15	

CPAP, continuous positive airway pressure; Am/FI, Amoxicillin and Flucloxacillin; IFN, interferon; IL, interleukin; CD, cluster of differentiation; Ig, immunoglobulin; C, complement.

50), Apgar-scores were 7 and 8 after 1 and 5 min respectively, and presented with generalized edema and short penis (about 1 cm). The ventral foreskin of the penis was connected to the scrotum after pushing back the penis, and the testes were palpable in both scrotums. The second-born infant (twin B) weighed 1830 g (percentile < 10) and had an Apgar score of 7 in 1 min and 8 in 5 min. After birth, they were both tachypneic and showed retraction signs, neonatal respiratory distress syndrome (NRDS) was diagnosed (Table 1).

Peripheral blood was collected on the day after birth for TORCH detection. CMV-IgM was positive (2.7 COI, reference range  $\leq 1.0$  COI) in twin A while negative (0.15 COI) in twin B. Levels of CMV-IgG of both twin increased, which were 237.1 U/m in twin A and 359.3 U/ml in twin B respectively (reference range  $\leq 1$  U/ml) (Fig. 1). Specific IgG of rubella virus in both twin A and B increased, but the level of IgM was normal. The IgG and IgM levels of toxoplasma gondii and HSV-1/2 in twins were in the normal range. Serology for hepatitis B, hepatitis C, HIV and treponema pallidum were negative. Preliminary tests showed that the twin A probably had acquired intrauterine CMV infection, but the infection of the twin B could not be ruled out. In order to determine whether the twins were infected and the potential effects on the organ development during pregnancy, more examinations were performed.

Blood and urine of the twin A for CMV-DNA detection by the quantitative PCR (qPCR) were undertaken on the 2nd day after birth, the results showed  $2.21 \times 10^4$  /ml in urine while negative in blood. Detection of CMV-DNA in saliva on the 3rd day was also positive ( $1.45 \times 10^5$  copies/ml). Results of reexamination of CMV-DNA before discharge were still positive in urine and saliva, the twin A was diagnosed with congenital CMV infection. As for the twin B, detection of CMV-DNA on the 8th day in blood, urine and saliva were both negative. CMV status of the mother after parturition demonstrated negative IgM and positive IgG (256.9 U/ml), and the detection of

**Fig. 1.** Detection of serum CMV-IgM and CMV-IgG in twins after birth.

CMV-DNA in blood, urine and breast milk were negative (Table 2). Data concerning her CMV status before pregnancy or during second or last trimester could not be retrieved.

Laboratory investigations showed a normal white cell count, differentiation, hemoglobin level and platelet count in twins. For twin B, level of aspartate transaminase (AST) increased on the 1st day and returned to normal on the 7th day, and total bilirubin physiologically elevated from the 3rd day. Both twin A and B presented a normal urine routine and renal function. Under conventional treatment without antiviral drug, digestive function of the twins gradually improved. Immune function tests were shown in Table 1. For cytokine profiles, the results demonstrated that the serum levels of interleukin (IL)-10 and IL-6 in both twins were increased. As for distribution of lymphocyte subsets, similar absolute counts of cluster of differentiation (CD)3 lymphocyte were showed in twins, CD4 T-lymphocyte count in twin A was less than that of twin B whereas CD8 count was higher. The total serum IgG levels of the twins were lower than the reference range. The results showed an increased level of serum CMV-IgM in twin A while the total serum IgM level remained in a relative low level.

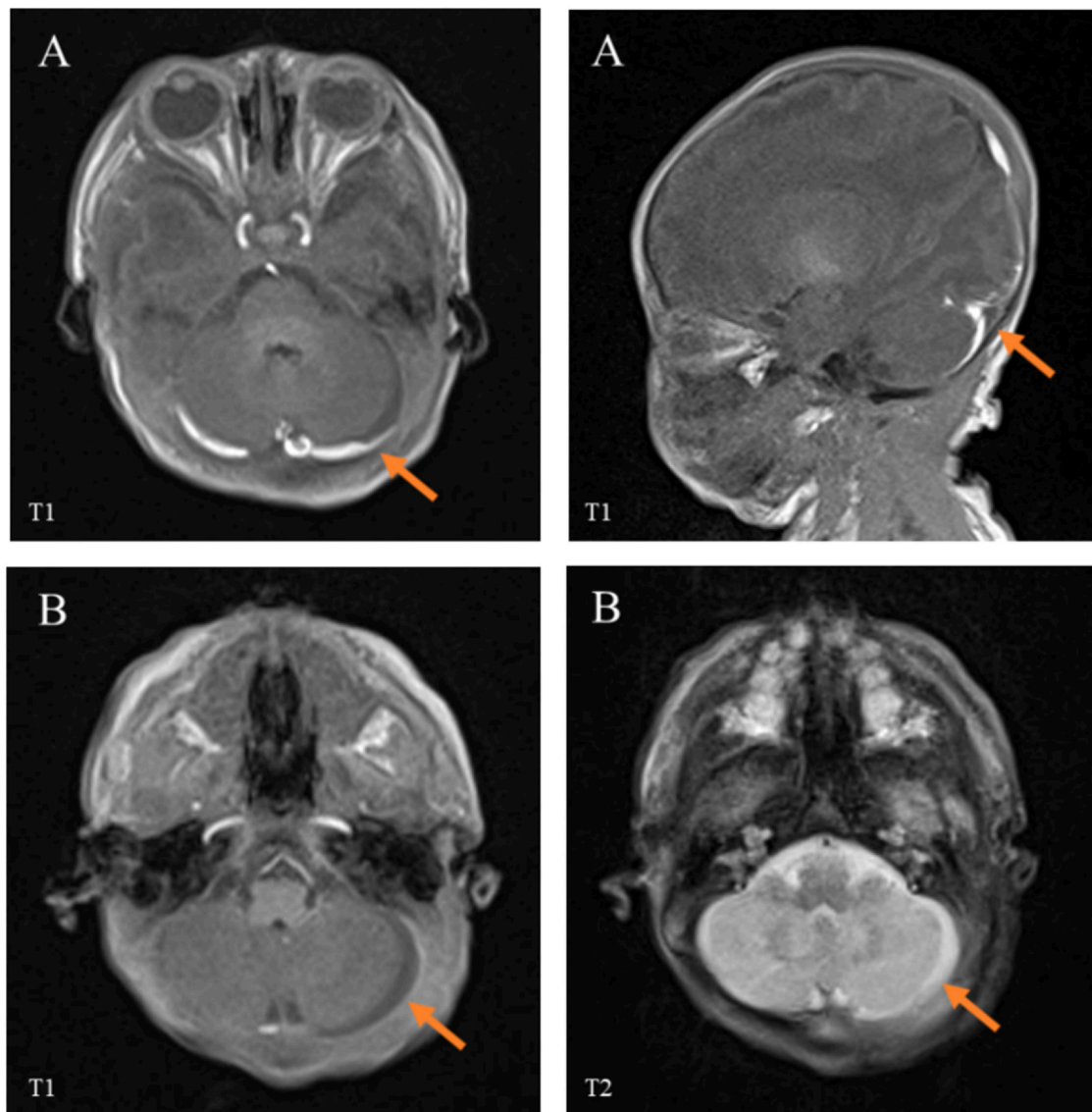
Chest X-ray of the twins showed ground-glass opacity in lungs fields, which was consistent with the performance of NRDS. Brain magnetic resonance imaging (MRI) revealed subarachnoid hemorrhage in twin A and occipital subdural effusion in twin B (Fig. 2a,b). Ultrasound of liver, spleen and heart showed no structural abnormalities. The twins were treated with nasal continuous positive airway pressure (nCPAP), amoxicillin and flucloxacillin for 3 days. Fundus examination and hearing screening at 1 week were normal. They were hospitalized on the 9th day (twin A) and 11th day (twin B) respectively.

After discharge, we continued to follow up with their virologic test, development and functions of important organs (Table 2, Fig. 3a-e). The twins came to visit in a good general condition and had been gradually gaining weight. According to the negative results of CMV-IgM and CMV-DNA in twin B during hospitalization and the first visit after discharge, CMV infection was ruled out. And he had achieved catch-up growth without any symptoms until 108 days. As for twin A, although in normal development and no obvious symptoms observed, CMV-DNA in urine continued to be positive and on the rise, and CMV-DNA in blood turned to be positive on the last visit. Besides, level of liver enzyme increased when compared to that of during hospitalization.

This study was approved by the Medical Ethical Committee of Zhongnan Hospital of Wuhan University, clinical ethical approval number 2020004.

## Discussion

Congenital CMV infection in twin pregnancy has high uncertainty and variable clinical outcomes. It is generally accepted that



**Fig. 2.** Brain magnetic resonance imaging (MRI) of the twins. Subarachnoid hemorrhage in twin A and occipital subdural effusion in twin B.

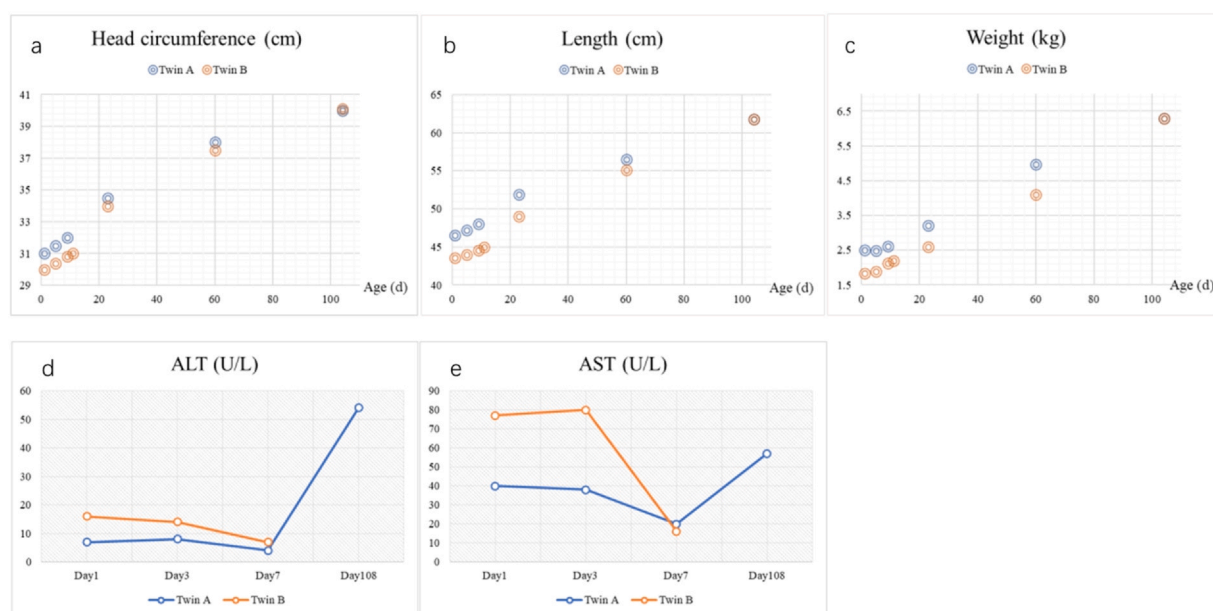
symptomatic congenital CMV infection occurs almost exclusively after primary maternal infection while infants are usually asymptomatic at birth in cases of recurrent maternal infection where maternal antibodies could partially protect fetus and reduce the possibility of severe fetal damage. Even though most of congenital CMV infected infants are asymptomatic at birth, few of them could develop delayed sequel, especially hearing loss in the long-term. In this case, despite the negative results of CMV IgM of the mother during the first trimester and after parturition, level of CMV IgG doubled after parturition compared to that during the first trimester. Thus, we supposed the mother had a primary CMV infection before this pregnancy, and had a recurrence during second or last trimester.

This case conformed to the diversity of clinical manifestations in CMV-infected twins. The dichorionic diamniotic twins in our case presented with intrauterine discordant growth and nonspecific symptoms of premature after birth. Unlike most cases reported in the past decades, it was the uninfected infant (twin B) who was small for gestational age (SGA, BW < 10th percentile) with the birth weight 670 g less than infant A (26.8%). The infected infant (twin A) who was appropriate for gestational age (AGA) seemed to be asymptomatic with congenital CMV infection, showed nonspecific symptoms of premature. Laboratory investigations showed a normal

blood routine and coagulation in twins. A temporary increase of AST was found in twin B. Immune function analysis demonstrated that there was no significant difference between the levels of serum immunoglobulin and cytokines in this dichorionic diamniotic twins, but the absolute value of CD8 T cells of twin A was higher. Brain MRI revealed subarachnoid hemorrhage (SAH) in twin A and occipital subdural effusion in twin B. The twins passed the fundus examination and hearing screening on 7th day, they had mild clinical symptoms and quickly recovered. As reported in literature, prognosis was not completely in accordance with clinical symptoms in twins with intrauterine CMV infection, we continued to follow up to evaluate outcomes in the long-term. The twins are in normal development without symptoms related to CMV disease. Ophthalmological and hearing reassessment at 3 month of age were normal. However, CMV-DNA in urine of the twin A continued to be positive, CMV-DNA in blood turned to be positive on the last visit (108 Days), level of liver enzyme increased. Antiviral drugs were not recommended for asymptomatic CMV infection. Different congenital CMV infection in dichorionic diamniotic twins is a remarkable feature of our case, the mechanism have not been appropriately illustrated in previous studies. Twin pregnancies are divided into monozygotic twins and dizygotic twins, which can be described as

**Table 2**  
Virologic Tests.

	Preganancy	Hospital stay					Follow up			
		12weeks	Day1	Day2	Day4	Day6	Day8	Day23	Day60	Day108
<b>Twin A</b>	CMV-IgM ( COI )		Positive/2.7	Positive/2.44				Positive/1.28		
	CMV-IgG ( U/ml )		Positive/237.1	Positive/223.7				Positive/159		
	CMV-DNA in Blood ( /ml )			Negative			Negative		Negative	Positive 1.77E+ 02
	CMV-DNA in Urine ( /ml )			Positive 2.21E+ 04		Positive 7.05E+ 03		Positive 4.89E+ 03	Positive 5.15E+ 05	Positive 8.94E+ 05
<b>Twin B</b>	CMV-IgM ( COI )		Negative/ 0.145	Negative/ 0.147				Negative/ 0.155		
	CMV-IgG ( U/ml )		Positive/359.3	Positive/311.6				Positive/200.9		
	CMV-DNA in Blood ( /ml )						Negative			
	CMV-DNA in Urine ( /ml )						Negative			
<b>Mother</b>	CMV-IgM ( COI )	Negative/0.124		Negative/ 0.143				Negative		
	CMV-IgG ( U/ml )	Positive/126		Positive/256.9						
	CMV-DNA in Blood ( /ml )			Negative						
	CMV-DNA in Urine ( /ml )			Negative						
	CMV-DNA in Breast milk ( /ml )				Negative					

**Fig. 3.** Growth and levels of liver enzymes of the twins during follow-up. a, head circumference; b, body length; c, body weight, d, alanine transaminase (ALT); e, aspartate transaminase (AST).

monozygotic diamniotic and dichorionic diamniotic twins [5]. Based on literatures reviewed, the incidence of discordant CMV infection is different in monozygotic diamniotic and dichorionic diamniotic twins. CMV infection in both monozygotic and dichorionic twins can occur in only one fetus or both twins, clinical symptoms and prognosis were quite different (Table 3). In the 21 reported cases of congenital CMV infected twins [2–4,6–14], 10 cases (47.6%) were single infant infection, of which 3 cases (30%) were stillborn or died after birth, 2 cases (20%) were terminated. 11 cases (52.3%) were infected with both twins, 1 case of them both twins were stillbirths, one of twins in a case died after birth, twins in a case were terminated. Twins were both infected in most of the monozygotic diamniotic twins with the proportion of 75% (3/4), while the infection rate in dichorionic diamniotic twins was 47.1% (8/17).

Dichorionic diamniotic twins had a greater probability of differential infection and a higher risk (52.9%, 9/17) of adverse outcomes than monozygotic diamniotic twins (25%, 1/4). Clinical features of congenital CMV infection in twins presented with a variety of symptoms, including stillbirth, intrauterine growth retardation, jaundice, hepatosplenomegaly and hearing impairment. The number of CMV infected cells in the placenta may account for its severity [9]. A few cases had mild or asymptomatic symptoms, which may be related to the fetal immune response or the range of placental lesions and virus transmission [15].

Blood transmission is the most likely transmission route. CMV may spread by entering to the fetal circulation through the umbilical blood exchange. The twins have the same intrauterine environment, and it is still unclear how the placental blood exchange leads to the



**Table 3**  
Cases of congenital CMV infection twins in literatures.

Author	Reported (Year)	MA (Years)	GA (Weeks)	MC/DA Gender (A/B), CMV	DC/DA Gender (A/B), CMV	Clinical features intrauterine or at birth	Outcomes
Samedí VM	2016	22	32	Unknown, +/-	A, male/B, female, +/-	A, IUGR, B, asymptomatic	A, bilateral hearing loss, B, health
Egana-Ugrinovic G	2016	/	29	Unknown, +/-	Unknown, +/-	A, severe, B, severe, IUGR, postnatal death	A, severe CMV inclusions disease 3years.
		/	30	Unknown, +/-	Unknown, +/-	A, uninfected, B, severe, IUGR	A, health, B, severe CMV inclusions disease 2years
		/	32	Unknown, +/-	Unknown, +/-	A, IUGR, termination(33w), B, uninfected	B, health
		/	25	Unknown, +/-	Unknown, +/-	A, NTD, termination(22w), B, asymptomatic	B, health
		/	38	Unknown, +/-	Unknown, +/-	A, asymptomatic, B, uninfected	A, asymptomatic 6 years, B, health
Nakajima J	2015	34	24	Female, +/-	Female, +/-	Twin-to-twin transfusion syndrome	A, hearing loss at 9 months, B, health
Manzoni P	2014	27	28	Female, +/-	Female, +/-	Maternal HIV, A, asymptomatic, B, PPHN	A, B, health
Simioni C	2013	34	28	Female, +/-	Female, +/-	A, asymptomatic, B, uninfected, IUGR	A, B, Health
Tomasik T	2012	/	38	Male, +/-	A, female/B, male, +/-	A, severe, microcephaly, B, uninfected	A, died at 8th month, B, health
Wu HY	2011	38	36	Male, +/-	Male, +/-	A, normal, B, fetal demise	A, health
Griesmaier E	2010	/	28	Unknown, +/-	Unknown, +/-	Twin-to-twin transfusion syndrome	A, B, both neurodevelopmental delay
Yinon Y	2006	/	27	Unknown, +/-	Unknown, +/-	A, B, asymptomatic	A, B, health
		/	24	Unknown, +/-	Unknown, +/-	A, B, asymptomatic	A, B, health
		/	22	Unknown, +/-	Unknown, +/-	A, asymptomatic, B, termination(28w)	A, health
		/	31	Unknown, +/-	Unknown, +/-	A, B, termination(32w)	/
		/	22	Unknown, +/-	Unknown, +/-	A, B, utero death	/
Kawana K	2004	34	36	Unknown, +/-	Unknown, +/-	A, severe, B, mild	A, bilateral hearing loss, B, health
Manoura A	2006	32	32	Male, +/-	Male, +/-	A, severe, B, uninfected	A, CMV inclusions disease at 4month, B, health
Lazzarotto T	2003	23	34	A, female/B, male, +/-	A, female/B, male, +/-	A, utero death, B, normal	B, health
		24	36	Female, +/-	Female, +/-	A, B, asymptomatic	A, hearing loss, B, health

MC/DA, monochorionic-diamniotic; DC/DA, dichorionic-diamniotic; GA, gestational age; DC, discordant growth; IUGR, intrauterine growth retardation; NTD, neural tube defect; PPHN, persistent pulmonary hypertension of the newborn; MA, Mother age; w, weeks; /, no data.

inconsistent chance of infection of the twins [5,16]. In this study, the CD8 T cells of twin A were higher than that of twin B, suggesting that CMV replication may activate the cellular immunity of infant A. Serum total IgG and CMV-IgG of twin B were both higher than that of twin A, whether t B obtained higher levels of maternally specific antibodies thus inhibiting virus replication is not yet clear. Apart from the increased level of serum IL-6 and IL-10, the cellular and humoral immune function indexes of the two infants were mostly within the normal range [17]. Research on primary CMV infection in infants and adults with CMV infection showed that adults had a higher CMV-specific CD4 T cell response at the initial stage of infection, releasing a large amount of interferon to exert antiviral effect, while CD4 T cells were unresponsive in children under 2-year age. However, there is no significant difference in the function of CD8 T cells between infants and adults after infection of CMV [18], intrauterine infection is related to the temporary hypofunction of CD4 T cells in the fetus. As for this case, the CD8 T cells of twin A increased, suggesting that the partial function activation of CD4 cells may trigger specific anti-CMV cellular immunity.

In conclusion, CMV infection can present as differential congenital infection in twin pregnancy, with various clinical symptoms. Fetal cellular immune function may be involved in the pathogenesis. There are deficiencies in this article. It is a retrospective study based on a single rare case, the placenta was not examined and the fetus is not tested for CMV infection before delivery. Also, it lacks the analysis of CD4T and CD8T cell subtypes. Long-term follow-up of the twins are necessary. Data of relevant cases from multiple-centers should be collected and analyzed.

**Abbreviations**

Not applicable.

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**Authors contribution**

SF, PL collected the data, wrote this draft and input the literature reviews; PY reviewed and revised this paper and DZ conceptualized and revised this paper, summary the literature. All authors read and approved the final manuscript.

**Consent for publication**

Consent to publish this information was obtained from study participants and thier parents.Written informed consent was obtained from the patients and guarantees for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

**Ethics declarations**

Ethics approval and consent to participate.This study was approved by the Medical Ethical Committee of Zhongnan Hospital of Wuhan University, clinical ethical approval number 2020004.

**Declaration of Competing Interest**

No potential conflicts of interest.

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