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Analysis of TORCH results of retinal exudative changes in neonates

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视网膜渗出样改变新生儿TORCH结果分析

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摘要

目的:探索新生儿视网膜渗出样改变与围产期TORCH感染的关系以及视网膜渗出样改变患儿的TORCH感染特点。

方法:回顾性研究。选取2019-05/2023-03在我院行眼底病变筛查发现视网膜渗出样改变并进行TORCH检测的新生儿共612例,按照性别、月龄分组,对其TORCH检测的结果进行统计学分析,明确其感染特点,并比较各组的阳性率。

结果:612例新生儿视网膜渗出样改变的TORCH检测结果中,巨细胞病毒(CMV-IgG)阳性率最高(96.7%),其次为风疹病毒(RV-IgG),阳性率(73.9%)。可存在两种及三种病毒的混合感染,其中混合感染IgG阳性率最高达71.2%(RV-IgG和CMV-IgG)。不同性别的新生儿渗出样改变TORCH感染差异性无统计学意义($P>0.05$)。不同月龄的新生儿渗出样改变TORCH感染中RV-IgG和CMV-IgM差异具有统计学意义($P<0.05$)。

结论:围产期TORCH感染可能为引起新生儿视网膜渗出样改变的重要因素。各种感染的差异与性别无关,与不同月龄相关。

关键词:新生儿;TORCH感染;视网膜渗出

Abstract

• AIM: To explore the relationship between retinal exudative changes in neonates and perinatal toxoplasmosis, others, rubella, cytomegalovirus, and herpes simplex virus (TORCH) infections, as well as the characteristics of TORCH infection in neonates with retinal exudative changes.

• METHODS: Retrospective study. A total of 612 neonates with retinal exudative changes detected during ophthalmic screening in our hospital from May 2019 to March 2023 were selected. TORCH tests were performed on these neonates, and the results were subjected to statistical analysis to determine the infection characteristics. The neonates with retinal exudative changes were grouped by sex and age, the characteristics of TORCH infection were analyzed, and the positive rates were compared.

• RESULTS: Among the 612 neonates with retinal exudative changes, the highest positive rate was observed for cytomegalovirus (CMV-IgG) (96.7%), followed by rubella virus (RV-IgG) (73.9%). Mixed infections with two or three viruses were also observed, with the highest positive rate for mixed infection of RV-IgG and CMV-IgG reaching 71.2%. There was no statistically significant difference in TORCH infection among neonates of different sex ($P>0.05$). However, there were statistically significant differences in RV-IgG and CMV-IgM infections with retinal exudative changes among neonates of different age groups ($P<0.05$).

• CONCLUSION: Perinatal TORCH infection may be an important factor causing retinal exudative changes in neonates. The differences in various infections are not related to sex but are related to different age groups.

• KEYWORDS: neonates; TORCH infection; retinal exudation

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INTRODUCTION

With increasing attention to the study of ocular birth defects in neonates, ophthalmic screening in newborns has gradually become popular nationwide. In 2013, the "Technical Specifications for Children's Eye and Vision Health," developed by the National Health Commission of China, stressed that newborns with risk factors for eye diseases should be screened by ophthalmologists as soon as possible after birth, and that healthy children should have their first screening for eye diseases 28 to 30 d after birth[1]. Various retinal lesions, including retinal hemorrhage, retinal exudative changes, retinal pigmentation or depigmentation, and familial exudative vitreoretinopathy (FEVR), have been identified in newborns during retinal screening[2]. In a multicenter study of retinal screening in 199 851 newborns in China, 6.9% of newborns were found to have retinal exudative changes[2]. Retinal exudative alterations were detected in 38 970 full-term infants in Chongqing at a rate of 9.7%, which was second only to the most frequent retinal hemorrhage[3]. Currently, limited studies suggest that retinal periphery exudative changes in newborns may be a series of pathological changes caused by hypoxia and infection, and they may be associated with abnormal factors such as gestational diabetes, nuchal cord, and toxoplasmosis, others, rubella, cytomegalovirus, and herpes simplex virus (TORCH) infections[4]. In a clinical analysis of term neonates with retinal white lesions, viral infection during pregnancy was closely related to the occurrence of term neonates with retinal white lesions[5]. This study performed TORCH testing on newborns with significant retinal exudative changes detected during retinal examination and analyzed the results to explore the relationship between retinal exudative changes in neonates and perinatal TORCH infections, as well as the characteristics of TORCH infection in neonates with retinal exudative changes.

SUBJECTS AND METHODS

Subjects This study used a retrospective analysis. The newborns with retinal exudation changes were collected from the screening cases of neonatal fundus lesions in Women and Children's Hospital of Chongqing Medical University from May 2019 to March 2023. A total of 612 newborns with significant retinal exudative changes detected during retinal examination and subsequently subjected to TORCH testing were included in the study. Among them, there were 398 males (accounting for 65.0%) and 214 females (accounting for 35.0%). The age ranged from 6 days to 3 months, with an average age of 1.23±0.573 months. Ethical aspects of the studies were approved by the Medical Ethics Committee of the Chongqing Health Center for Women (No.2018012).

Methods Parents of newborns were educated and signed the informed consent before the examination. The data of gestational age, birth weight, delivery mode and neonatal Apgar score were recorded. Retinal examination was performed using binocular indirect ophthalmoscopy combined with the Retcam3 wide-field fundus imaging system produced by Clarity, USA. Newborns with retinal examination showing exudative changes in at least two quadrants of the retina were selected for TORCH testing with parental consent. All blood samples were tested in the Clinical Laboratory of Women and Children's Hospital of Chongqing Medical University. The results of TORCH testing were analyzed and grouped by sex and age to compare the characteristics of TORCH infection in different sexes and age groups.

Positive judgment: The pathogens tested for TORCH in our hospital mainly included toxoplasma (TOX), rubella virus (RV), and cytomegalovirus (CMV). The cutoff values for positive results were as follows:

Old instrument (chemiluminescence method): TOX-IgM ≥ 0.83 S/CO, TOX-IgG ≥ 1.6 IU/mL, RV-IgM ≥ 0.75 S/CO, RV-IgG ≥ 5 IU/mL, CMV-IgM ≥ 0.85 S/CO, CMV-IgG ≥6 AU/mL.

New instrument (electrochemiluminescence method): TOX-IgM ≥0.8 COI, TOX-IgG ≥1 IU/mL, RV-IgM ≥0.8 COI, RV-IgG ≥10 IU/mL, CMV-IgM ≥0.7 COI, CMV-IgG ≥ 0.5 U/mL[6].

Statistical Analysis Data analysis was performed using IBM SPSS20.0 Statistics. Measurement data were expressed as rates, and the comparison of rates was conducted using the Chi-squared test. Pearson's Chi-squared test was used when the theoretical frequency was greater than 5, and the continuity-corrected Chi-squared test was used when the theoretical frequency was between 1 and 5. Fisher's exact test was used when the theoretical frequency was less than 1. Bonferroni correction was applied for multiple comparisons, and the significance level was set at 0.05/6. Measurement data were expressed as $\bar{x} \pm s$, and $P<0.05$ was considered statistically significant.

RESULTS

TORCH test results of the 612 neonates with retinal exudative changes showed that if IgM was positive, the corresponding IgG for the specific virus was also positive. The positive rate of RV-IgM was 0.2% (1/612), the positive rate of CMV-IgM was 9.0% (55/612), and the positive rate of mixed infection (RV-IgM and CMV-IgM) was 0.2%. The positive rate of TOX-IgG was 5.9% (36/612), the positive rate of RV-IgG was 73.9% (452/612), and the positive rate of CMV-IgG was 96.7% (592/612). Two or three virus co-infections were observed, with the highest positive rate for mixed infection of RV-IgG and CMV-IgG reaching 71.2% (Table 1).

The positive rate of male TOX-IgG was 7.0% (28/398) and that of female TOX-IgG was 3.7% (8/214), and the difference was not statistically significant ($P>0.05$) in 612 neonates with significant retinal exudate changes. There was no RV-IgM positive rate in males, and the positive rate of RV-IgG was 74.1% (295/398). The positive rate of RV-IgM and RV-IgG in females was 0.5% (1/214) and 71.0% (152/214) respectively. There was no significant difference in the positive rate of RV infection between male and female ($P>0.05$). The positive rates of male CMV-IgM and CMV-IgG were 9.8% (39/398) and 96.5% (384/398), and the positive rates of female CMV-IgM and CMV-IgG were 7.5% (16/214) and 97.2% (208/214), respectively. There was no significant difference in the positive rate of CMV infection between male and female ($P>0.05$; Table 2).

There was no significant difference in the positive rates of TOX-IgG, RV-IgM and CMV-IgG among newborns with exudated altered TORCH infection in different age groups (all $P>0.05$). The highest positive rate of RV-IgG was 86.9% (53/61) in patients less than 1 month old, followed by 78.5% (329/419) in patients 1-2 months old, and 53.0% (70/132) in patients older than 2 months old. There were statistically significant differences in the positive rate of RV-IgG in newborns with exudate changes in different age groups ($P<0.05$). The CMV-IgM positive rate was 6.0% (25/419) at 1 to 2 months of age, and the highest CMV-IgM positive rate was 22.7% (30/132) at 2 months of age. The difference was statistically significant among different age groups ($P<0.05$). There were statistically significant differences in the positive rate of CMV-IgM between younger than 1 month and 1-2 months of age and older than 2 months of age ($P<0.05$), but there were no statistically significant differences in the positive rate of CMV-IgM between younger than 1 month of age and 1-2 months of age ($P>0.05$; Table 3). In TORCH positive children, peripheral exudative leukoplakia can be detected 1 day after birth. At the age of 1 month (Figure 1). The exudative leukoplakia gradually fused with clear boundaries (Figure 2). At 4 months of age, the boundary of the exudative leukoplakia was blurred and gradually absorbed (Figure 3). By 11 months of age, the exudative leukoplakia gradually fused into clumps and showed signs of disappearance (Figure 4).

Table 1 Characteristics of TORCH infection in neonates with retinal exudative changes (n, %)

Number of pathogens	Pathogen type	IgM positive	IgG positive
1	TOX	0	36 (5.9)
	RV	1 (0.2)	452 (73.9)
	CMV	55 (9.0)	592 (96.7)
2	TOX+RV	0	29 (4.7)
	TOX+CMV	0	36 (5.9)
	RV+CMV	1 (0.2)	436 (71.2)
3	TOX+RV+CMV	0	29 (4.7)

TOX: Toxoplasma; RV: Rubella virus; CMV: Cytomegalovirus.

Table 2 Characteristics of TORCH infection with exudate change in neonates of different sex (n, %)

Sex	TOX		RV		CMV	
	IgM	IgG	IgM	IgG	IgM	IgG
Male ($n=398$)	0 (0)	28 (7.0)	0 (0)	295 (74.1)	39 (9.8)	384 (96.5)
Female ($n=214$)	0 (0)	8 (3.7)	1 (0.5)	152 (71.0)	16 (7.5)	208 (97.2)
χ^2		2.732	1.863	0.676	0.918	0.224
P		0.098	0.172	0.411	0.338	0.636

TOX: Toxoplasma; RV: Rubella virus; CMV: Cytomegalovirus.

Table 3 Characteristics of TORCH infection in neonates with different months of age (n, %)

Months	TOX		RV		CMV	
	IgM	IgG	IgM	IgG	IgM	IgG
<1 ($n=61$)	0 (0)	5 (8.2)	0 (0)	53 (86.9)	0 (0)	59 (96.7)
1-2 ($n=419$)	0 (0)	20 (4.8)	1 (0.2)	329 (78.5)	25 (6.0)	403 (96.2)
≥2 ($n=132$)	0 (0)	11 (8.3)	0 (0)	70 (53.0)	30 (22.7)	130 (98.5)
χ^2		2.953	0.461	39.734	41.165	1.685
P		0.228	0.794	<0.001	<0.001	0.431

TOX: Toxoplasma; RV: Rubella virus; CMV: Cytomegalovirus.

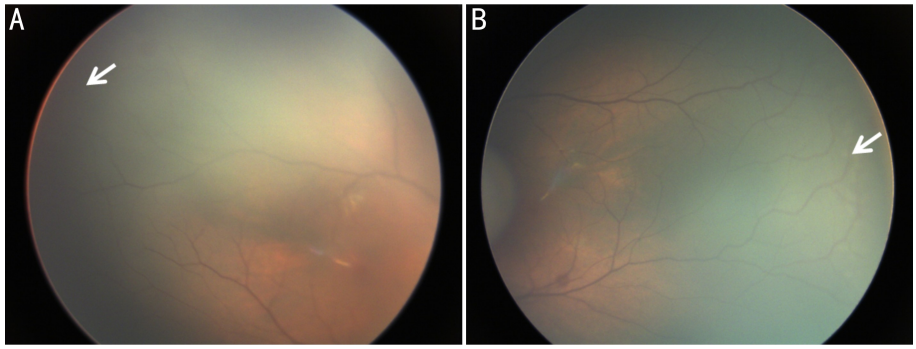

Figure 1 Neonatal fundus disease screening at day 1: retinal exudation with hemorrhage in both eyes. A: OD; B:OS.

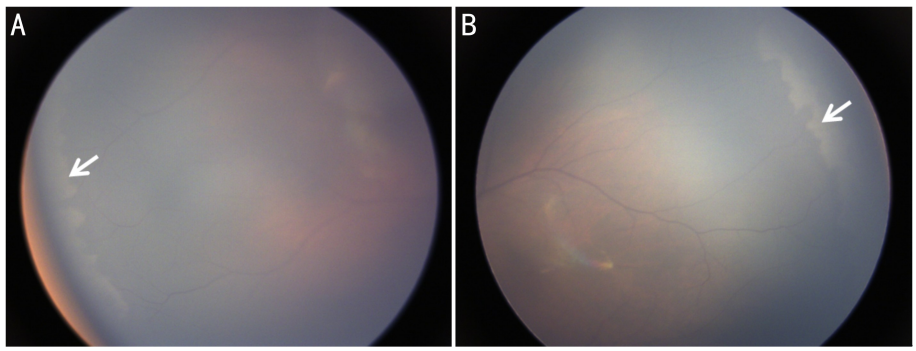

Figure 2 Reexamination at 1 month of age: retinal exudate changes in both eyes, TORCH: TOX-IgG 19.5 IU/mL (+), CMV-IgG 93.1 AU/mL (+). A: OD; B: OS.

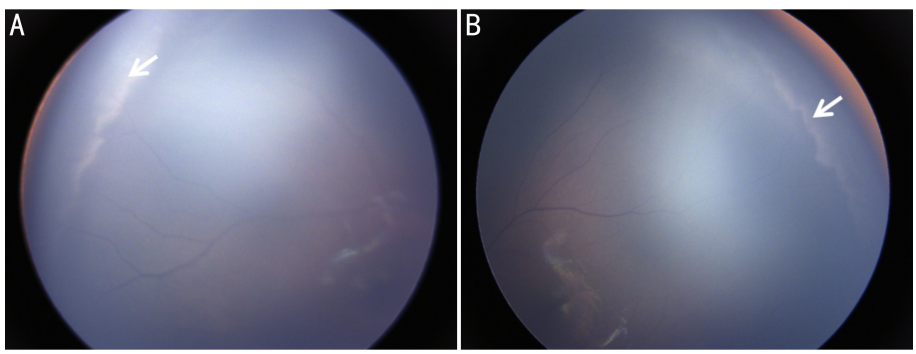

Figure 3 Reexamination at the age of 4 months: retinal exudation in both eyes gradually fused. A: OD; B: OS.

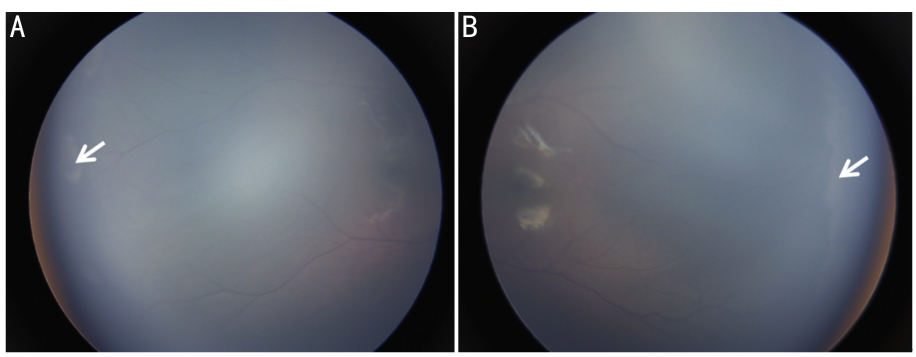

Figure 4 Reexamination of the patient at 11 months of age showed gradual absorption of retinal exudation in both eyes. A: OD; B: OS.

DISCUSSION

Retinal exudation in newborns is also clinically known as retinal white lesion or retinal leukoplakia[7]. According to the morphological results examined by Retcam III wide-area imaging system for infants and young children, it can be divided into 4 types: spot-shaped exudation, arc exudation, strip exudation and cluster exudation[8], among which the most common is spot-shaped exudation, and its etiology is still unknown. It is generally believed that gestational hypertension, gestational diabetes and umbilical cord around the neck can eventually lead to chronic fetal hypoxia[9], and chronic hypoxia can lead to acidosis, lysosomal rupture and cell autolysis, and ultimately necrosis of retinal capillary endothelial cells, which can lead to exudation. In clinical practice, through constant review of retinal exudation changes in newborns, it was found that with the passage of time, a few

dots and stripes of white lesions could gradually disappear by themselves from 3 to 6 mo after birth, while some clusters of white lesions showed a trend of gradual fusion and gradual absorption, as shown in Figures 1-4. Currently, children with more exudation changes in the retina (3-4 quadrants) were observed. It even takes two to 3 years after birth to gradually disappear. In this study, the positive rate of TORCH infection was as high as 99.4% in newborns with retinal exudative changes, among which CMV infection was the most common, followed by RV infection and the mixed infection of CMV and RV. Studies have shown that retinal exudative changes in infants and young children are associated with CMV infection, and 11.1% of children with CMV infection have retinal exudative changes in fundus examination[10]. Human retinal pigment epithelium (hRPE) cells are important cells in establishing and maintaining human eye immune function. They are the target cells of human cytomegalovirus (hCMV), but are able to limit viral replication. The hCMV can cause opportunistic posterior uveitis, such as retinitis and chorioretinitis[11-12]. Studies have shown that hCMV induces pro-inflammatory cytokines and angiogenic cytokines in periretinal cells. In IBRB, pericytes may act as amplifying reservoirs that promote retinal inflammation and angiogenesis[13]. A recent study using single-cell RNA-Seq has demonstrated that placental cells express NRP2, PDFGRA and CD46 receptors, which permit CMV invasion to host cells[14]. Different retinal development phenomena occur throughout the gestational period, as well as postnatally, different outcomes are expected depending on the infection period[15]. Therefore, perinatal infection with CMV is likely to lead to retinal inflammation, followed by neo.

In this study, we investigated the relationship between retinal exudative changes in neonates and TORCH infections. Our results showed a high prevalence of TORCH infections in neonates with retinal exudative changes, suggesting a possible association between these infections and the development of retinal lesions in newborns.

Among the TORCH pathogens, CMV showed the highest positive rate, followed by RV. Mixed infections of RV and CMV were also observed, indicating the coexistence of multiple viral infections in some cases. These findings suggest that TORCH infections, particularly CMV and rubella, may play a significant role in the development of retinal exudative changes.

Sex did not appear to be a significant factor influencing TORCH infection rates in neonates with retinal exudative changes. However, we observed significant differences in RV-IgG and CMV-IgM infections among neonates of different age groups. This suggests that the risk of TORCH infection may vary with age, highlighting the importance of timely screening and intervention in different age groups. In the primary infection of TORCH, specific IgM antibodies are first present, followed by IgG antibodies, so clinically positive IgM usually represents a recent infection and IgG represents a past infection[16]. IgG can cross the placenta, so it is possible that only IgG positive may be caused by infection in the mother or by infection of the fetus itself. IgM cannot cross the placenta, so a positive IgM can be seen as the result of a neonatal infection or an intrauterine infection of the fetus[17-18]. The positive rate of RV-IgG in different age groups was less than 1 month, followed by 1-2 months of age and more than 2 months of age. The reason may be that RV-IgG infection is mostly transmitted from the mother through the placenta and is manifested in neonatal serum, and its titer gradually decreases with the increase of neonatal age. The difference of CMV-IgM showed that it gradually increased with the increase of age, and IgM could not pass through the placenta, so it could be inferred that there was CMV infection, and the possibility of the infant's own infection was high. TORCH infection is called syndrome in perinatal medicine, and these viruses are highly harmful and widespread in daily living environment[19].

The results of this study contribute to a better understanding of the relationship between TORCH infections and retinal exudative changes in neonates. The positive titer of CMV-IgG with retinal exudate changes in newborns was as high as 300-400 U/mL or more, and the relationship between the specific titer and the shape and severity of retinal exudate changes is still under further study. However, there are some limitations to consider. The study focused solely on neonates with significant retinal exudative changes, which may not represent the entire population of neonates with TORCH infections. Additionally, further research is needed to explore the mechanisms underlying the association between TORCH infections and retinal lesions.

In conclusion, perinatal TORCH infections, especially CMV and rubella, may be significant factors contributing to the development of retinal exudative changes in neonates. This study emphasizes the importance of TORCH screening in newborns with retinal lesions and highlights the need for early intervention to prevent potential visual impairments associated with these infections.

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