Case Report

THRESHOLD RETINOPATHY OF PREMATURITY IN CYTOMEGALOVIRUS- INFECTED INFANT: A CASE REPORT

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ABSTRACT

The relationship between the development of retinopathy of prematurity (ROP) and cytomegalovirus (CMV) infection is not well understood. We report a case of Type I threshold ROP in a CMV-infected premature infant. A female infant born via normal delivery at 30 weeks gestational age with a birth weight of 1.65 kg was diagnosed with bilateral stage 3 ROP zone 2 with plus disease. She was treated with peripheral retinal photocoagulation 48 hours after diagnosis. As this patient appear not to have strong enough cause for a threshold ROP further investigations were performed to exclude other risk factors that could contribute to severe ROP. Laboratory reports revealed CMV antigens in the infant's urine and CMV immunoglobulin G(IgG) in the mother's blood. Antiviral treatment was not initiated, as the infant had no other systemic manifestations. Subsequently, the ROP regressed after laser treatment. This case supports a few other reports associating CMV-infected infants with severe ROP. Thus, suspicion of CMV infection or CMV-infected mothers should alert clinicians of the possibility of severe ROP development in premature infants. Concurrent CMV infection in premature infants or mothers may be associated with the development of severe ROP.

INTRODUCTION

Retinopathy of prematurity (ROP) is a proliferative retinopathy that primarily affects premature and low-birth-weight (LBW) infants. Other risk factors for ROP have also been identified, including oxygen supplementation, sepsis, intraventricular haemorrhage, anaemia, use of surfactants, and assisted conception. Human cytomegalovirus (CMV) infections are one of the potential risk factors for ROP that have been described, but reports are scarce. While most CMV infections are asymptomatic, in immunosuppressed patients and infants, particularly premature infants, severe illness may occur and lead to blindness, hearing loss, defects in the central nervous system and growth restriction [1]. The relationship between CMV infection and ROP in premature infants is however not clearly understood. This case report describes the development of a Type 1 threshold ROP in a CMV-infected infant.

CASE PRESENTATION

We report a case of a 32 weeks gestational age (GA) female infant weighing 1.65 kg, born via normal delivery after premature prelabour rupture of membrane (PPROM). Following delivery, the infant received 56 hours of supplemented oxygenation via continuous positive airway pressure (CPAP), with the highest oxygen concentration of 30% followed by 15 days of intermittent oxygenation via a nasal cannula. Subsequently, the infant was able to saturate in room air. The patient also had Grade 1 intraventricular haemorrhage (IVH) diagnosed at birth. She was monitored in the neonatal intensive care unit (NICU) till she reached a target weight.

The infant was seen for ROP screening at 34 weeks gestational age (GA). Fundus examination of the right eye revealed arteriolar tortuosity and venous dilatation at the posterior pole in all quadrants, presence of ridges with neovascular tufts from 4 to 11 clock hours and pre-retinal haemorrhage at 7 o'clock in zone II. However, vascularization had already occurred up to zone III at 12 to 1 clock hours. (Figure 1). The left fundus showed similar findings of dilated tortuous vessels in all quadrants with ridges and neovascular tufts from 1 to 8 clock hours as well as pre-retinal haemorrhage at 2 o'clock in zone II. Similarly, retinal vascularization occurred up to zone III at 10 to 12 clock-hour (Figure 2). There was no iris vessel engorgement, the pupil dilated well with mydriatic agent. The vitreous was clear, no retinal detachment seen. The anterior segment findings were normal.

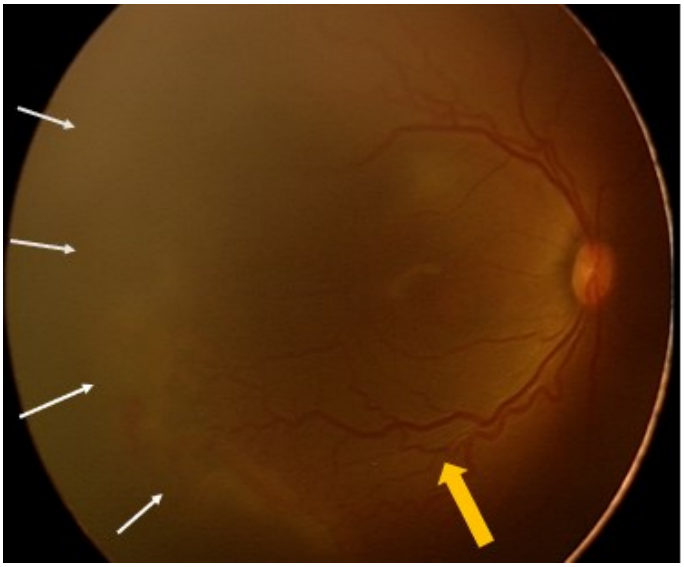

Figure 1: Right fundus showing dilated tortuous vessels in the posterior pole in all quadrants (yellow arrow), presence of ridges with neovascular tufts from 4 to 11 clock hours(white arrows)

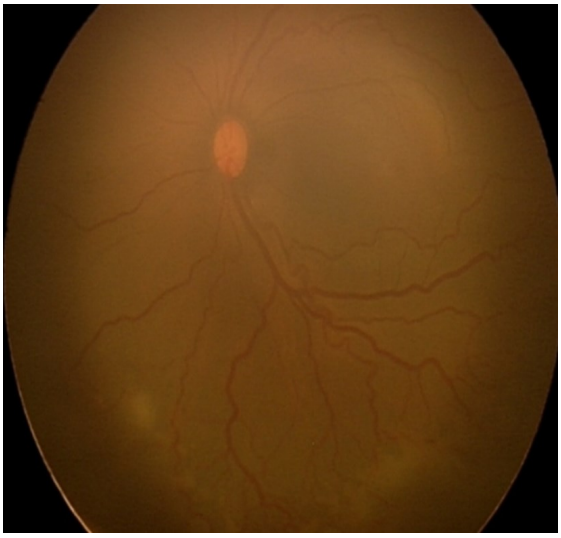

Figure 2: The left Fundus: dilated tortuous vessels in all quadrants with ridge and neovascular tufts.

Based on the findings a diagnosis of Bilateral stage 3 ROP zone II with plus disease, a Type 1 threshold disease was made. The diagnosis was based on the International Classification of Retinopathy of Prematurity 2005 and Early Treatment for Retinopathy of Prematurity (ETROP) [2,3]. Peripheral retinal photocoagulation therapy via laser indirect ophthalmoscopy (LIO) was successfully performed 48 hours after the diagnosis.

Low birth weight, prematurity, oxygen supplementation, grade 1 intraventricular haemorrhage, and neonatal jaundice were identified as risk factors contributing to the development of ROP in this case. However, we observed that these risk factors were not strong enough to cause a threshold ROP. This prompted the investigation to rule out any other potential risk factors. The patient was screened for CMV, as this virus was reported to cause worsening of ROP in the past [4]. The results revealed that CMV virus particles were detected in the urine via polymerase chain reaction (PCR); however, no CMV antibodies were detected in the blood. The cerebrospinal fluid (CSF) samples and placental histopathology were also negative for CMV. The mother was tested as well as she could be the source of infection. The mother tested positive for CMV immunoglobulin G (IgG) but negative for immunoglobulin M (IgM) and viral PCR. Auditory assessment and cranial ultrasonography done to look for other CMV infection sequelae were normal.

Antiviral treatment was not considered in this patient as there was no evidence of chorioretinitis or other organ involvement. In addition, the investigations were carried four weeks after birth. Diagnosis of congenital CMV is made within two–three weeks of age, beyond this period, breastmilk transmission is still possible because the mother breastfed the child.

Ten days after the peripheral laser photocoagulation, the ROP showed regression, as evidenced by the flattened ridge, resolved pre-retinal haemorrhage, and less vascular tortuosity (Figure 3). Early laser treatment is a crucial factor in regression of the lesion. The infant was under regular ophthalmology follow-up for ROP monitoring and paediatric follow-up for growth assessment.

DISCUSSION

Is cytomegalovirus infection related to severity of ROP? Little is known about their relationship, even though it is well known that each independently causes significant mortality and morbidity in premature infants. In the past, threshold ROP was defined by the CRYO-ROP study group as the degree of ROP severity which indicates the need for treatment. However, later randomised trial on early stages of ROP by Early Treatment for Retinopathy of Prematurity group (ETROP) demonstrated better outcomes if ROP were treated earlier than the threshold stage. Prethreshold ROP can be divided into two types: Type 1 which is high risk, and Type 2, low risk ROP. Based on this study, treatment is recommended to reduce unfavourable outcomes in type 1 prethreshold ROP rather than to wait for threshold ROP to occur [3]. The risks of developing more severe types of ROP are higher with lower gestational age and lower birth weight [5].

Immature infants have the most significant risk of acquiring an early and symptomatic CMV infection, which can be transmitted via antenatal transfer, intrapartum, or breastfeeding [1]. CMV infection in the eye commonly manifests as chorioretinitis. Optic atrophy, macular scarring, or cortical damage are sequelae that may lead to blindness. In addition, CMV causes mental retardation and hearing loss.

In this case, we observed that other risk factors that led to the development of threshold ROP were low. Even though categorised under LBW group according to the World Health Organization (WHO) classification and late preterm group [6], the child was not under the extreme group of both classes. Even though oxygen supplementation via a ventilator was administered, the duration was short. A multivariate analysis reported that children on longer ventilation of more than 28 days have a 4.07 times higher risk of developing Stage 3 to 4 ROP than those with lesser ventilator exposure [7]. This infant had Grade 1 intraventricular haemorrhage (IVH) diagnosed at early birth; however, higher grades of IVH are more at risk of developing ROP of stage 3 or worse [8]. Poor association was found between neonatal jaundice and ROP development [9].

Tagami et al. described a case of severe symptomatic congenital cytomegalovirus, which presented as posterior vessel dilatation, demarcation line at zone III, and arteriovenous anastomosis without chorioretinitis features similar to this case. However, they considered CMV-related retinopathy as the primary diagnosis and ROP secondary to foetal growth restriction as the differential diagnosis. After completing a systemic Valganciclovir course, the lesions regressed, leaving behind the macula and peripapillary chorioretinal atrophy [10]. In contrast, another study comparing the sequelae of CMV-infected premature infants reported no significant difference in ROP development in CMV-infected infants compared to uninfected infants [11].

We postulated that in our case, CMV infection may contribute to the acceleration of ROP, even without systemic manifestations. The pathophysiology of the development of retinopathy is not clear; however, the CMV virus was hypothesised to cause anti-migratory and anti-angiogenic effects, affecting vasculogenesis and cause loss of pericyte

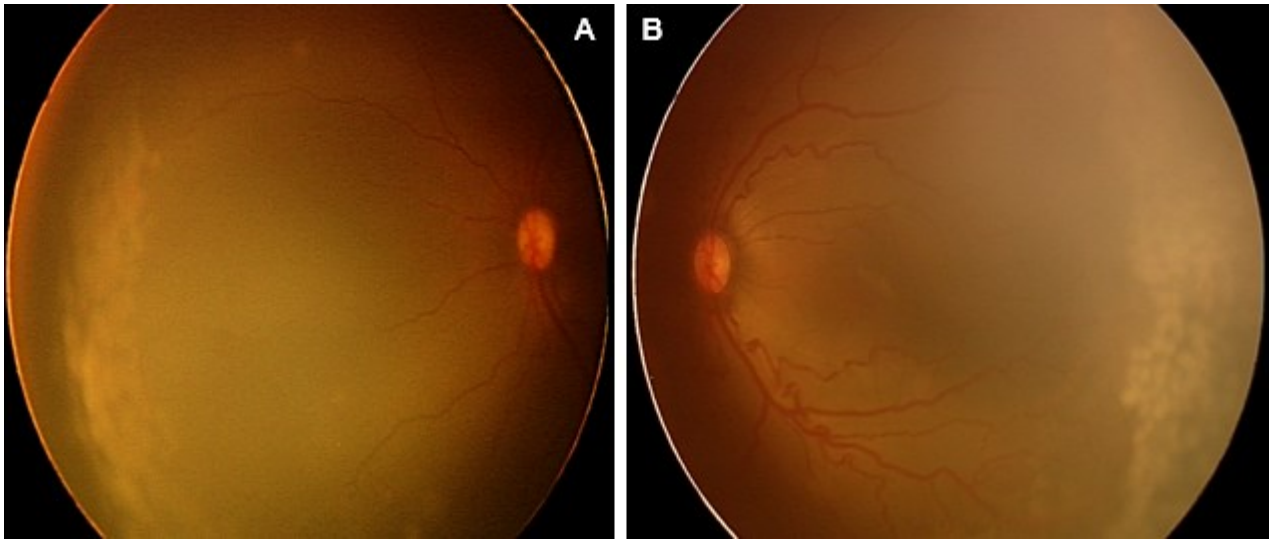

Figure 3: A) Right fundus and B) Left fundus ten days after peripheral retinal photocoagulation, showing ROP regression, evidenced by flattened ridge, resolved pre-retinal haemorrhages, and less vascular tortuosity.

at proximal sites within the retinal vasculature [12,13]. In our case, laser treatment was effective and sufficient even without antiviral therapy for underlying CMV infection. Routine screening of CMV virus might be helpful if similar scenarios are encountered. This would be beneficial not only for ocular diagnosis but also for detecting other occult systemic involvement of CMV infection. The suspicion of CMV infection or CMV-infected mothers should alert clinicians to the possibility of severe ROP development in premature infants. Further studies are needed to explore and support these findings.

CONCLUSION

Concurrent CMV infection in the infant or mothers may be associated with development of severe ROP in premature infants. We report this case in the hope to create awareness and aid in early diagnosis and subsequent management of similar cases.

CONFLICT OF INTEREST

The author(s) declare no potential conflicts of interest concerning the research, authorship, and publication of this article. This case has been presented as e-poster in Asian Pacific Vitreo-Retinal Surgery (APVRS) Scientific Meeting 2022

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