

CASE REPORT

pISSN: 1907-3062 / eISSN: 2407-2230

Childhood blindness from surge of advanced stage retinopathy of prematurity in premature infants during the COVID-19 pandemic: a case series

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ABSTRACT

BACKGROUND

Retinopathy of prematurity (ROP) is a proliferative disease of the ocular retinal vasculature in premature infants, being a leading cause of preventable childhood blindness. The COVID-19 pandemic serves as an additional barrier to access to care and referral, potentially leading to more cases of advanced stage ROP. Although surgery can be done, ROP at this stage is highly associated with poor functional outcome irrespective of surgery. This case series aims to report advanced stage (stage 5) ROP in premature infants during the COVID-19 pandemic.

METHODS

A retrospective case series of medical records of paediatric patients with ROP was performed at Cipto Mangunkusumo National Referral Hospital between March 1, 2020 and December 31, 2021. This case series included new patients that presented to our clinic from March 2020 to December 2021 with stage 5 ROP.

RESULTS

A total of 19 eyes of 10 patients with stage 5 ROP were included in this study. Mean chronologic age at presentation to our referral centre was 7.0 ± 4.0 months. Upon presentation, all had stage 5 ROP with negative blink reflex to light, and none of the eyes in this cohort underwent surgical intervention. Mean gestational age was 30.3 ± 3.2 weeks and mean birth weight was 1,276.7 ± 366.4 g.

CONCLUSION

There was an observable surge of stage 5 ROP at our referral centre with irreversible blindness. This highlights the need for proper ROP screening in all hospitals in Indonesia to prevent delay in detection and care of advanced stage ROP.

Keywords: Retinopathy of prematurity, Stage 5 ROP, COVID-19, ROP screening, childhood blindness

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Date of first submission, December 20, 2022

Date of final revised submission,
November 9, 2023

Date of acceptance, November 16, 2023

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Cite this article as: Yulia EY, Soeharto DA. Childhood blindness from surge of advanced stage retinopathy of prematurity in premature infants during the COVID-19 pandemic: a case series. *Univ Med* 2023;42:360-7. doi: 10.18051/UnivMed.2023.v42:360-367



INTRODUCTION

Retinopathy of prematurity (ROP) is a proliferative disease of the retinal vasculature of the eye in premature infants, and serves as one of the leading causes of preventable childhood blindness.⁽¹⁾ Indonesia has a relatively high prevalence of advanced stage ROP.^(2,3) Late detection of ROP may lead to presentation of advanced stage ROP which gives rise to potential childhood blindness.

Stage 5 ROP is defined by the International Classification of Retinopathy of Prematurity (ICROP) as total retinal detachment. This stage can be divided into three subcategories: Stage 5A, when the optic disc is observable through ophthalmoscopy; Stage 5B, when the optic disc cannot be seen due to the presence of closed-funnel detachment or retrolental fibrovascular tissue; and Stage 5C, which includes features of Stage 5B along with abnormalities in the anterior segment.⁽⁴⁾ Although surgery can be done in stage 5 ROP, the disorder at this stage is highly associated with poor functional outcome despite surgery, thus potentially resulting in childhood blindness. A previous review showed that the postoperative visual outcome of stage 5 ROP is largely limited, because even with relatively successful anatomical re-attachment, visual improvement after surgery is still very poor and limited. Moreover, recurrence of detachment in stage 5 ROP is as high as 22%. Thus, the functional prognosis of patients with stage 5 ROP despite being given intervention is poor.⁽⁵⁾

With the high incidence of ROP in Indonesia and the understanding of the importance of screening, it would be expected that the Coronavirus disease 2019 (COVID-19) pandemic in the beginning of 2020 along with its large-scale lockdowns may impact detection of ROP, be it from the patients' perspective or the limited capacity of healthcare infrastructure to continue optimal screening services during the massive surge of COVID-19 patients. In this period, demands exceeded available resources leading

to the collapse of healthcare systems in Indonesia. The first documented COVID-19 case in Indonesia was on the 1st of March 2020, and full nationwide lockdown (referred to as the 2020 large-scale social restriction or *pembatasan sosial berskala besar*) was implemented on the 17th of April 2020, with the second nationwide lockdown (community activities restrictions enforcement or *pemberlakuan pembatasan kegiatan masyarakat*) implemented on the 11th of January 2021.⁽⁶⁾ Other countries have reported that the pandemic led to a significant decline in ophthalmic outpatient visits as well as procedures.⁽⁷⁻⁹⁾ Notably, an unpublished study conducted in our hospital found that although there was a 55% decline in outpatient visits in the year 2020, there was a substantial increase in high risk ROP patients, from 27.5 % in 2019-2020 to 53.2% in 2020-2021. Thus, the objective of this study was to report on new cases of advanced stage (stage 5) ROP that presented to our hospital during the COVID-19 pandemic.

METHODS

Study design

A retrospective case series was performed at the Paediatric Ophthalmology clinic at Cipto Mangunkusumo National Referral Hospital between March 1, 2020 and December 31, 2021.

Participants

The inclusion criteria of this case series were new patients that presented to our clinic from March 2020 to December 2021 with stage 5 ROP. Incomplete medical records were excluded from this study. Informed consent was obtained from all parents of the study subjects, and this study was conducted in accordance with the Declaration of Helsinki. We recorded and evaluated the patients' demography, gender, age, laterality, place of birth, delivery history, gestational age (GA), birth weight (BW), birth length, ROP risk factors, as well as surgical management if any.

ROP screening and management

A senior paediatric ophthalmic surgeon (DEY) with 10 years of experience examined all eligible neonates using a binocular indirect ophthalmoscope and +20 D lens under topical anaesthesia with 0.5% tetracaine hydrochloride eye drops. The newborns' eyelids were separated with an infant wire speculum, and a wire vectis was utilized as a scleral depressor. To fully dilate the pupils, three drops of 0.5% tropicamide + 2.5% phenylephrine ophthalmic solution were instilled simultaneously. Retinopathy of prematurity was graded into stages and zones according to ICROP.⁽⁴⁾ Patients with stage 5 ROP were eligible for inclusion in this study, in which management involves routine monitoring. Surgical intervention is rarely performed in stage 5 ROP due to poor prognostic outcome regardless of surgical intervention.

Statistical analysis

Analysis was done on the characteristics of the subjects, and quantitative data was described as mean (standard deviation) or median (min-max), depending on the normality of the given data as determined by the Kolmogorov-Smirnov test. Categorical variables were presented as frequency and percentage, n (%). Data was managed using Microsoft Office Excel version 16.55 and analysed using IBM SPSS (Statistical Package for the Social Sciences) version 26.

Ethical clearance

Informed consent was obtained from all study subjects, and this study was conducted in accordance with the Declaration of Helsinki. Ethical approval is not required for case series at our institution.

RESULTS

The total number of ROP cases at our institution during the pandemic period of 2020-2021 comprised of 59 patients over the span of two years. In comparison, data of ROP cases in the years prior to the pandemic lock-down period

was 27 patients in the span of two years (2018-2019). A total of 19 eyes of 10 patients with stage 5 ROP that newly presented to our hospital in the years 2020-2021 were included in this study, with all patients except one having bilaterally involved eyes. As shown in Table 1, almost all patients with stage 5 ROP (8/10, 80%) were born outside of Jakarta, with the furthest being from East Nusa Tenggara. Mean chronologic age at presentation to our referral centre was 7.0 ± 4.0 months with an age range of two to 15 months and mean post-menstrual age of 58.3 ± 16.8 weeks. Females accounted for slightly more than half of the study population (6/10, 60%). Upon presentation at our centre, all 19 eyes presented with stage 5 ROP, with the exception of one patient with unilateral ROP. All patients presented with a negative blink reflex to light. None of the eyes in this cohort underwent surgical intervention.

Patients were mostly born via caesarean section (6/11, 60%), with mean gestational age of 30.3 ± 3.2 weeks and gestational age range of 24 to 35 weeks. Mean birth weight was $1,276.7 \pm 366.4$ grams, with the lowest birth weight being 724 grams and the heaviest being 1,900 grams. As for birth length, the mean was 41.6 ± 5.2 cm, and the range was from 36 to 48 cm. All patients had a history of inpatient care at a Neonatal Intensive Care Unit (NICU), with mean NICU stay being 22.9 ± 10.4 days, and all were noted to have a history of oxygen therapy. None of the patients in this cohort underwent ROP screening during their NICU stay in their originating hospital, with the exception of one patient from East Nusa Tenggara, a rural province outside Java, that was screened for ROP at birth and initially referred, although the patient's parents did not follow through with the treatment or the referral of their child, noting the pandemic as their reason for not seeking treatment.

DISCUSSION

In the current study, the authors sought to evaluate the real effects of the COVID-19 pandemic lockdown on ROP screening in the

Table 1. Patient characteristics

Gender	Chronologic age (months)	PMA (weeks)	Birth Place	ROP Stage	GA (weeks)	Method of birth	Birth weight (grams)	Birth length (cm)	Duration in NICU (days)
Female	2	35	Tangerang, Banten	5 ODS	27	SC	724	37	38
Male	3	44	North Jakarta, DKI Jakarta	5 ODS	32	PV	1,775	47	10
Female	5	48	Sukabumi, West Java	5 OD	28	PV	1,150	37	24
Male	3	42	Sintang, West Kalimantan	5 ODS	30	SC	1,100	36	20
Female	9	68	Kupang, East Nusa Tenggara	5 ODS	32	SC	1,100	48	37
Male	8	63	Pangkal Pinang, Bangka Belitung	5 ODS	31	SC	1,500	42	12
Female	15	92	Bogor, West Java	5 ODS	32	SC	1,310	43	30
Female	11	68	Pringsewu, Lampung	5 ODS	24	PV	908	36	14
Male	6	56	Bekasi, West Java	5 ODS	32	PV	1,900	48	30
Female	8	67	West Jakarta, DKI Jakarta	5 ODS	35	SC	1,300	N/A	14

Note: PMA: postmenstrual age; ROP: retinopathy of prematurity; GA: gestational age; ODS: oculo dextra et sinistra; NICU: neonatal intensive care unit; SC: Sectio caesarea; PV: per vaginam

Paediatric Ophthalmology clinic at Cipto Mangunkusumo National Referral Hospital, Jakarta. The incidence of ROP at our institution during the pandemic period of 2020-2021 was 59, which was higher than the incidence in the years before the pandemic with an incidence of 27 in the years 2018-2019. In April of 2020, Indonesia implemented its first full nationwide lockdown, and a second lockdown in January of 2021.⁽⁶⁾ During this period, our hospital continued with patient services while strictly implementing health protocols that were in place at the time. This included conducting COVID-19 screening, maintaining physical distance in clinical settings, and wearing appropriate personal protective equipment (PPE) according to COVID-19 zonation at our hospital. Furthermore, initial patient screening was conducted with priority being given towards screening of ROP for premature babies that presented to our hospital.

Retinopathy of prematurity is considered to be a prominent cause of childhood blindness.⁽¹⁰⁾ Low- to middle-income countries (LMIC) have experienced an increase in ROP occurrence within the last decade, which may be due to improvements in the survival rate of premature infants.⁽¹¹⁾

Previous studies have observed that LMICs such as Indonesia detected ROP in infants above 32 weeks GA which is not often seen in high-income countries (HICs).^(12,13) In our study, the average GA at birth was 30.3 ± 3.2 weeks, with five out of ten patients having a GA of 32 weeks or higher. A study on stage 5 ROP in a referral centre in China with patients also from rural areas of the country had comparable findings, with mean GA of 32.1 ± 2.2 weeks and a range of 28-36 weeks, with 80% of their infants being born at 30-34 weeks.⁽¹¹⁾ By contrast, a study in the United States on patients with stage 5 ROP reported a mean GA of 28 ± 3 weeks.⁽¹⁴⁾

In terms of BW, the patients in our cohort had a higher BW in comparison to previous studies in HICs. The average BW in our study was $1,276.7 \pm 366.4$ grams, with the lowest being 724 grams and the largest being 1,900 grams, whereas a previous study in the United States noted that the mean BW with stage 5 ROP was $1,100 \pm 363$ grams.⁽¹⁴⁾

This suggests that although a high risk of severe ROP is often associated with lower BW and younger GA, as in previous studies showing that larger birthweight (>750 grams) and higher GA (>30 weeks) were associated with the absence of ROP,^(15,16) the findings in our study suggest that advanced stage ROP can also occur in neonates that do not present classically as small or very premature, namely premature infants that are older or have higher BW. Another study in Turkey supports this notion in that severe ROP may be found in heavier premature infants.⁽¹⁷⁾

Apart from BW and GA, other risk factors for advanced stage ROP include longer duration of oxygen therapy;^(18,19) with our study cohort having an average NICU stay with oxygen therapy of 22.9 ± 10.4 days. Several studies have established that oxygen fluctuations are a recognized risk for ROP, with oxygen fluctuations at several time durations up to 30 days following birth increasing the odds of a preterm infant developing severe ROP.⁽²⁰⁾ Another study revealed that infants given oxygen therapy or ventilation for seven days or more had a higher risk of ROP progression.⁽²¹⁾

A previous study reported that in their cohort of stage 5 ROP, patients who were inborn (defined as born at the study's centre and not referred from an outside centre) were significantly associated with the absence of ROP.⁽¹⁷⁾ By contrast, 80% of our cohort were referred from outside of Jakarta, particularly from rural provinces throughout Indonesia, and none of the patients were screened for ROP during their hospital stay in their province of origin. This implies that screening for ROP may not be equally available in rural areas in Indonesia, which contributes to delay in ROP detection thus leading

to presentation of advanced stages of ROP. This was implied in another study in China on stage 5 ROP which reported that all patients were born outside of their study centre, and the majority of their cohort were referred from medical centres in rural provinces that were not equipped with proper ROP screening facilities.⁽¹¹⁾

The key method of preventing ROP is early detection by conducting eye screening in infants at risk for ROP, which according to the Indonesian National Guideline for Screening and Treatment of ROP includes those born at 34 weeks and younger, having a birth weight of 1,500 grams or lower, or in those with high risk factors for ROP such as excessive oxygen therapy.⁽¹⁾ During the pandemic period, our hospital continued to conduct ROP screening and management according to the ROP screening and management guidelines⁽¹⁾ while strictly abiding by the health protocols, which included conducting COVID-19 screening on patients prior to ROP screening, practicing strict hand hygiene, sanitization of screening equipment, and complying with appropriate PPE guidelines according to COVID-19 zonation at our hospital.⁽²²⁾

A multi-centre survey in Indonesia found that the rate of ROP screening (number of premature infants that were screened for ROP) in non-academic hospitals (government and private hospitals) was 19-42%, in comparison with 86-93% at referral or academic hospitals,⁽³⁾ thus implying that resources and facilities for appropriate ROP screening may differ among hospitals. In other countries, similar findings were reported, such as those of an Indian study reporting that gaps in timely screening, referral, and treatment were noted in their cohort of stage 5 ROP patients, with an overall delay in first examination for ROP of 24.7 ± 3.9 weeks.⁽²⁰⁾ A study in Saudi Arabia also reported suboptimal implementation of screening guidelines, with physician unavailability or lack of skills being the most common reason.⁽²³⁾ Comparably, the mean chronologic age at presentation to our hospital was 7.0 ± 4.0 months, with a range of two to 15

months. Apart from differences in resource and physician availability in Indonesia in allowing for proper ROP screening, the COVID-19 pandemic also further emphasizes the potential delay in seeking care and physician shortage.⁽⁷⁻⁹⁾ This was exemplified with one of our patients whose parents noted the pandemic as their reason for not being able to seek treatment or referral.

All patients in our cohort presented as irreversibly blind with negative blink reflexes to light. When ROP is detected at stage 5, surgery may be considered despite the fact that poor visual prognosis can be expected even with treatment. In the ETROP study, of eleven eyes with stage 5 ROP that underwent vitreoretinal surgery, more than half resulted in no light perception post-surgery.⁽²⁴⁾ Another review reported that the rate of successful anatomical results post-surgery was only 20-50%, and even then, improved visual acuity was minimal, with various studies reporting variable post-operative visual acuity.⁽²⁵⁾ Moreover, final macular attachment rate in another study was only 19%, owing to high rates of re-detachment.⁽²⁶⁾ Hence, stage 5 ROP has poor functional prognosis irrespective of treatment.

The limitations of our study comprise the relatively small number of patients included. However, this number of patients is still important as it serves as a reflection of the number of potential childhood blindness that can occur in advanced stage ROP. Moreover, to our knowledge, this is the first study in Indonesia to focus on stage 5 ROP as a study population. This study might not accurately reflect the incidence of ROP or how the pandemic has affected ROP in Indonesia. The study does, however, draw attention to the fact that ROP is a major concern in the region and to the substantial impact the pandemic has had on the screening program. Future studies are needed in order to further highlight the importance of early detection of ROP to prevent childhood blindness.

CONCLUSION

In conclusion, there was an observable surge

at our referral centre of stage 5 ROP with irreversible blindness. This highlights the need for proper ROP screening in all hospitals in Indonesia to prevent delay in detection and care of advanced stage ROP.

ACKNOWLEDGEMENT

Not applicable

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

CONTRIBUTORS

All authors take public responsibility for the content of the manuscript submitted to *Universa Medicina*. DEY supervised the entire process of this study, and contributed to the initial concept and idea. DEY and DAS contributed to the conception and design of the study, data acquisition, analysis and interpretation, as well as manuscript preparation, editing and review. All authors have read and approved the final manuscript.

FUNDING

This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

DATA AVAILABILITY STATEMENT

Not applicable.



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