Original Article

Prevalence, risk factors and pattern of severe retinopathy of prematurity in eastern Madhya Pradesh

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Purpose: To describe the prevalence, characteristics including risk factors, and pattern of severe ROP from eastern Madhya Pradesh region of India. **Methods:** In this 5-year retrospective study, Baseline characteristics, systemic risk factors, and findings of ROP screening were noted. Factors associated with severe ROP including aggressive posterior ROP (APROP), stage IV and V ROP were analyzed. Statistical analysis was done using SPSS version 20. **Results:** Of 763 babies screened, 30% were diagnosed to have ROP. Prevalence of severe ROP was 14.2% (109) of which 60 (55.5%) were classic and 30 (27.7%) were APROP. Eighteen (16.6%) were diagnosed as advanced ROP (stage IV and V). Mean gestational age (GA) and birth weight (BW) for severe ROP were 31.05 weeks and 1.34 kg, respectively which were inversely associated with severe ROP. But a significant 10% of severe ROP were seen in late preterm babies, >34 weeks. Low GA and respiratory distress syndrome (RDS) were significant risk factors for APROP. Most important factor for stage IV and V ROP was late presentation for screening. **Conclusion:** The study found a high prevalence of severe ROP including APROP. Almost 7% severe ROP cases were outside screening guidelines of NNF. Late presentation for screening is the most important factor associated with ROP related blindness.

Key words: Aggressive posterior ROP, Retinopathy of prematurity, Risk factors of ROP, ROP blindness, Severe ROP

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World Health Organization has identified Retinopathy of Prematurity (ROP) as an important cause of blindness in both high- and middle-income countries.[1] Clinical profile of ROP is very different in developed and developing world. In developing countries including India, several reports have suggested that clinical profile of severe ROP is different from their western counterparts.[1-6] There is variation in the incidence of ROP even in urban and rural centers of India.[7] Most of the available data on severe ROP in India is from urban or developed parts of the country. Data are lacking from less-developed areas, which has recently seen an increased survival of pre-term neonates due to improvement in neonatal health care facilities backed by UNICEF. With increased survival, prevalence of ROP is expected to rise and that of severe ROP also. Hence, there is a need to study the risk factors for severe ROP in these areas which if taken care of, can be a step towards decreasing the burden of this disease.

This study was designed to evaluate the prevalence, pattern, and risk factors for severe ROP requiring therapy. Thus, the authors retrospectively analyzed 5 years data on ROP of infants who were admitted and screened in a tertiary care institute of central India that caters to a predominantly rural population.

Methods

A retrospective data analysis of records of all babies screened for ROP between August 2012 and March 2018 was done. Most of the babies were born or referred immediately after birth from district or sub-district level hospitals to our tertiary level care Special New born Care Unit in a government Medical College located in east Madhya Pradesh. All babies were screened according to screening protocol of the institute i.e., screening of all preterm babies <37 weeks gestational age and <2 kg birth weight at 4 weeks. Additionally, term babies with an unstable postnatal course, those for whom screening was recommended by pediatrician within 4 weeks of age and some babies presenting outside this time period were also included in this study. Level of prematurity of screened babies was defined as extreme preterm (<28 wks, very preterm (28–32 wks), moderately preterm (33–34 wks), late preterm (35–37 wks), and term (>37 weeks). Baseline characteristics noted for all babies were mother's name, sex, gestational age, birth weight, age at the time of first screening, and being small/appropriate for gestational age (SGA/AGA). Risk factors analyzed in the study included respiratory distress syndrome (RDS), neonatal hyperbilirubinemia (NNH), neonatal sepsis (NNS), birth asphyxia, necrotizing enterocolitis (NEC), multiple gestation, shock, Rh incompatibility, hypocalcemia, hypothermia, patent ductus arteriosus (PDA), apnoea, hypoglycemia, and gastro-intestinal hemorrhage (GIH). Findings of ROP screening were noted as no ROP, mild ROP defined as not requiring treatment and severe ROP cases defined as requiring laser

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treatment or referral to higher centre for surgery. For further risk factor analysis, no ROP cases were excluded and mild ROP cases were compared with severe ROP. Severe ROP included all babies of threshold ROP as defined by CRYO–ROP study, prethreshold type I ROP as defined by ETROP study, aggressive posterior ROP (APROP) and all cases diagnosed as advanced ROP (Stage IV and V) at the time of first screening.[8,9] All cases of severe ROP were further categorized as classic ROP and aggressive posterior ROP both of which are laser treatable and advanced stage ROP, requiring surgery. Risk factors for APROP were analyzed by comparison with severe classic ROP cases.

Statistical analysis

Data were analyzed using software SPSS version 20. Qualitative variables were analyzed using chi square test, quantitative variables were analyzed using student *t* test. *P* value was calculated and a value <0.05 was considered as significant. Univariate analysis was done for the risk factors associated with severe ROP. Multinominal logistic regression model was made for risk factor analysis associated with severe ROP.

Results

A total of 763 babies were screened between August 2012 and March 2018 of whom 309 (40.4%) babies were female and 314 (41.2%) were small for gestational age. Mean gestational age (GA) of screened babies was 33.28 ± 0.105 (SEM 95% CI) (range 26-40 weeks) and mean birth weight (BW) was 1.63 ± 0.015 (SEM 95% CI) (range 0.6–3.6 kg). The mean age at the time of first screening was 4.67 weeks ± 0.095 (SEM 95% CI) (range 1–24 weeks). Amongst all screened babies, ROP was seen in 230 (30.1%) babies. Mild ROP was present in 121 (15.8%) and severe ROP in 109 (14.2%) babies [Fig. 1]. Timely screening i.e., within 4 weeks of birth, was done in 481 (63%) babies out of total study cohort.

A total of 109 cases were diagnosed with severe ROP, out of which 60 (55.5%) presented like classic ROP with stage 1 (2), 2 (26), 3 (31) in various zones. Thirty (27.7%) were diagnosed as APROP with features of peripheral ill-defined retinopathy, flat neovascularization, intraretinal shunting, and plus disease located in zone I or posterior zone II. One baby was detected to have hybrid form of ROP showing stage 2 nasally and APROP like features temporally. Amongst all severe ROP cases, 59 (54.1%) received a timely screening for ROP and rest presented late. Eighteen (16.6%) of the total severe ROP cases were diagnosed as advanced stage of ROP right at the time of first screening none of whom received a timely screening for the disease and all presented late between 5 and 24 weeks of age. Of these 7 were stage 4a, 2 had stage 4b and 9 were detected to have stage 5 ROP i.e., total retinal detachment. Location of severe disease was analyzed in which 31.49% were in zone I, 51.85% were in zone II, none in zone III. In the remaining babies, zone could not be defined due to advanced stage ROP.

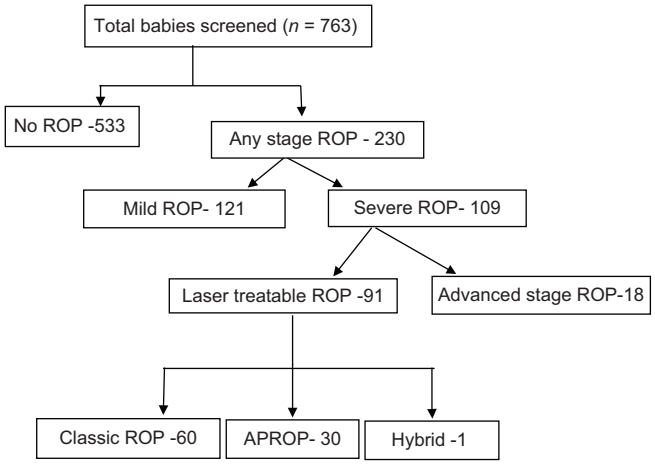

Figure 1: Flowchart showing distribution of ROP

The baseline characteristics of babies with severe ROP are summarized in Table 1. Low gestational age was found to be significantly associated with severity of ROP (p =<0.003). However, a significant proportion of severe ROP was also seen in late preterm babies (≈10%) and one term baby (38 wk GA) was found to have severe ROP in zone II anterior, requiring treatment. Most of the babies of severe ROP had birth weight in the range of 1–1.5 kg but almost 6.5% of them had a birth weight of >2 kg. The age at the time of presentation was found to have a significant impact on severity of ROP as evidenced by the fact that almost 46% (50) of severe ROP cases presented late for screening with a mean age at screening of 6.06 weeks.

Comparing the mild and severe ROP cases for univariate risk factor analysis of severe ROP, it was seen that RDS, multiple gestation, shock, gastrointestinal hemorrhage, and thrombocytopenia were seen more frequently in severe ROP group compared to mild ROP group but none of them showed a statistically significant difference between both groups. Only low gestational age, birth weight, and late presentation for screening were found to be significantly correlated with severe ROP [Table 2]. Multivariate logistic regression analysis was done to further analyze risk factor associations with severe ROP and it was found that birth weight had the strongest association with severe ROP followed by age of presentation and gestational age. Birth weight and gestational age were

Table 1: Baseline characteristics of severe ROP cases

Characteristics of severe ROP	Results
Total cases (*n*)	109
Females (%)	47.7
Mean gestational age (weeks, mean±SEM 95% CI)	31.05±0.11 (range 26-38 wks)
Mean birth weight (kg, mean±SEM 95% CI)	1.34±0.04 (range 0.6-3.15 kg)
Mean age at presentation (weeks, mean±SEM 95% CI)	6.06±0.46 (range 1-24 wks)
Small for gestational age (%)	33.9
Gestational age (%)	
Extreme preterm (<28 wks)	4.6
Very preterm (28-32 wks)	67.9
Moderately preterm (33-34 wks)	17.4
Late preterm (35-37 wks)	9.2
Term (>37 weeks)	0.9
Birth weight (%)	
<1 kg	10.2
1-1.5 kg	61.1
1.5-2 kg	22.2
>2 kg	6.5

inversely associated with incidence of severe ROP as they had negative regression coefficient while age of presentation was directly related to severe ROP [Table 3].

In subgroup analysis of cases it was found that aggressive posterior ROP (APROP) contributed significantly to severe ROP with 27.7% (30) cases. The mean gestational age and birth weight of APROP babies were 30.9 weeks and 1359.9 gm respectively. The gestational age of this group was found to be significantly lower than the classic ROP group ($P = 0.015$). The major proportion of APROP cases (83.3%) were less than 32 weeks gestational age, but a significant (16.7%) proportion were also of gestational age more than 32 weeks. Sex and being SGA was not found to be associated with APROP. On

Table 2: Risk factors for severe ROP; Univariate analysis (Chi square/T-test)

Risk factor	Mild ROP	Severe ROP	Significance (*P*)
Females %	43.8	47.7	0.553
Mean gestational age (weeks) (mean±SEM 95% CI)	32.8±0.24	31.05±0.28	<0.001
Mean birth weight (KG) (mean±SEM 95% CI)	1.59±0.04	1.34±0.04	<0.001
Mean age at presentation (weeks) (mean±SEM 95% CI)	4.32±0.15	6.06±0.41	<0.001
SGA %	43.8	33.9	0.13
RDS%	51.2	62.4	0.09
NNH %	25.6	25.7	0.99
NNS %	31.4	30.3	0.85
Asphyxia %	10.7	7.3	0.39
Twins %	17.4	22.9	0.29
Shock %	28.9	33.9	0.41
NEC %	5.8	2.8	0.26
Thrombocytopenia %	2.5	6.4	0.14
Rh-incompatibility %	0.8	1.8	0.50
Apnoea %	5.0	4.6	0.90
PDA %	0.0	2.8	0.07
Hypothermia %	0.8	1.8	0.50
Hypoglycemia %	2.5	5.5	0.24
G I Hemorrhage %	1.7	3.7	0.34
Hypocalcemia %	0.8	1.8	0.50
CHD %	0.8	2.8	0.27

Table 3: Risk factors related to severe ROP; Multivariate logistic regression analysis

Parameter	Regression coefficient	Standard error	Wald χ^2	OR (95% CI)	Significance (*P*)
Birth weight	-1.18	0.50	5.50	0.31 (0.12-0.82)	0.02
Age at presentation	0.20	0.08	6.82	1.23 (1.05-1.43)	0.01
Gestational age	-0.18	0.09	4.267	0.84 (0.71-0.99)	0.04
Rh-incompatibility	-2.79	1.57	3.15	0.06 (0.003-1.34)	0.06
Hypocalcaemia	-1.91	1.33	2.07	0.15 (0.01-1.99)	0.15
CHD	-1.55	1.93	0.65	0.21 (0.01-9.25)	0.42
Hypothermia	-1.02	1.32	0.60	0.36 (0.02-4.76)	0.44
RDS	-0.60	0.34	3.18	0.55 (0.28-1.06)	0.08
Thrombocytopenia	-0.50	0.97	0.27	0.60 (0.09-4.04)	0.60
Twins	-0.50	0.30	1.58	0.61 (0.28-1.32)	0.21
Hypoglycaemia	-0.49	0.93	0.28	0.61 (0.10 - 3.81)	0.60
G I Haemorrhage	-0.34	1.03	0.11	0.72 (0.10 - 5.35)	0.74
NNS	0.26	0.37	0.52	1.23 (0.64-2.65)	0.48
Sex	0.21	0.33	0.41	1.23 (0.65-2.33)	0.52
NNH	-0.18	0.38	0.23	0.55 (0.28-1.06)	0.63
Shock	-0.17	0.37	0.21	0.84 (0.41-1.75)	0.65
NEC	-0.16	0.97	<0.01	0.98 (0.15-6.54)	0.10
AGA/SGA	0.14	0.49	0.08	1.15 (0.44-2.98)	0.78
Apnoea	-0.07	0.76	0.01	0.93 (0.21-4.07)	0.92
Asphyxia	-0.02	0.57	<0.01	0.98 (0.32-2.96)	0.97

comparing risk factors between APROP and severe classic ROP cases, RDS was found to be significantly associated with the development of APROP. Observing the annual trends, the prevalence of APROP was seen to have increased substantially over the years which accounted for almost 50% of total severe ROP cases in recent years.

The prevalence of blindness and severe visual impairment (Stage IV and V) in our cohort was 2.2%. The mean gestational age was 28.05 weeks and mean birth weight was 1.11 kg. All presented late for screening with their mean age at first screening being 12.38 weeks (range 5–24 weeks). Out of 9 babies with bilateral stage V ROP, 5 were brought by parents with white reflex and non-fixation and had never been screened before for ROP, one baby was timely screened by general ophthalmologist but declared normal (false screening) and three babies were referred by ophthalmologist for leucocoria or congenital cataract.

Discussion

This study conducted in a government institute in eastern Madhya Pradesh catering mostly to rural population, highlights the high incidence of severe ROP in this region. The incidence of ROP in this study was 30%, which was comparable with reports from various other parts of India which documented an incidence between 20-51.9%.[10-13] However, the 14% incidence of severe ROP in the present study is much higher than other reports.[14,15]

A higher prevalence of severe ROP was reported by Charan *et al.* and Rekha *et al.*, but these studies were done more than two decades ago and there has been an improvement in neonatal practices since then.[10,11] This should have led to a decreased incidence of ROP but this does not seems to be the case and even recent reports show highly variable rates of severe ROP in different centers. Kumar *et al.* have reported a 4.7% incidence of severe ROP[14] and Vinekar *et al.* documented severe-ROP requiring treatment in 3.5%.[15] On the other hand Hungi B *et al.* and Ahuja *et al.* have reported a higher incidence of 10.2% and 13.2% of severe ROP respectively.[7,16] This is an indication that neonatal care is highly variable in different parts of our country and there is a great divide in developed and less developed parts. This high incidence in the current study may also be a sign of high oxygen dose given to babies because of non-availability of oxygen blenders in SNCU's, established under NHM in hospitals in Madhya Pradesh.

Not only the prevalence rates but patient profile was also different. Mean birth weight and gestational age of severe ROP cases in this study were 1.34 ± 0.04 (SEM 95% CI) kg and 31.05 ± 0.28 (SEM 95% CI) weeks respectively which were higher than Kumar *et al.* (1113 ± 436 g and 29 ± 2.7 weeks, respectively).[14] Though low gestational age and lower birth weight were found to be significantly associated with severe ROP in the present study, a significant proportion (≈10%) of severe ROP cases were relatively more mature (late preterm; >34 weeks) and 6.5% of severe ROP cases had more than 2 kg birth weight. A term baby (38 wks) with 3.15 kg birth weight developed severe ROP in zone II anterior with plus disease and was treated with laser. Kumar *et al.* have reported, very few babies with gestational age more than 32 weeks and none with birth weight greater than 2 kg, developing severe ROP.[14] The development of severe ROP in babies outside the recommended screening criteria (i.e., >34 weeks and >2 kg) is a matter of concern. This may direct us to change our protocol regarding new-born management and screening for ROP and also gives us an area of future research to know why. It also highlights the importance of keeping the "third criteria" in mind for screening of bigger babies.[17]

The authors did not find any statistically significant risk factors for severe ROP other than BW, GA, and age of presentation which could be because in this study, severe ROP cases were compared with mild ROP cases and not with no ROP as done in other studies. Severe ROP and mild ROP groups were closely similar to each other in this study and although factors like multiple gestation, shock, gastrointestinal hemorrhage, and thrombocytopenia were seen more frequently in severe ROP, they did not reach statistical significance.

Mean age at presentation of severe ROP cases was significantly higher than mild ROP cases and none of the patients with advanced stages of ROP were screened timely. On annual trend analysis, a definite decline in the age of presentation for screening was observed from an average of 14 weeks in the beginning to 4.66 weeks in recent years.

On multivariate logistic regression analysis birth weight was found to be most strongly associated with severe ROP. From this finding it can be inferred that for the same level of prematurity lesser the birth weight more is the chance of developing severe ROP. Multivariate analysis done in other studies found respiratory distress syndrome, low gestational age, and patent ductus arteriosus as significant factor associated with severe ROP which was different from our study and this could be because they used no ROP as controls while this study used mild ROP as controls.[14]

It was observed that almost 28% of total severe ROP cases were APROP. This number is significantly higher than other studies. Kumar *et al.* have reported Zone I disease to be very uncommon with only one baby in their cohort.[14] Hungi B *et al.* have reported 13.2% of ROP cases were APROP in a rural neonatal intensive care unit.[7] The mean gestational age and birth weight of APROP babies in this study (30.9 weeks and 1359.9 gm, respectively) were higher than reported by Sanghi *et al.* (29.75 weeks and 1259.66 gm).[18] In the present study lower gestational age and presence of RDS were significant risk factors for development of APROP as compared to classic form of severe ROP. Of all babies of APROP, 5 (16.7%) babies in APROP group were more than 32 weeks gestation. Sanghi *et al.* also encountered 9.1% babies of APROP who were born after completing 32 weeks of gestation in their cohort.[18] On observing the annual trend in this study it was found that the proportion of APROP cases were continuously rising, with no cases in 2012 rising up to 50% of severe ROP cases in 2017. Early screening of very premature babies in recent years could be one of the factors responsible for more diagnosis of APROP. In the past, these babies were not timely diagnosed and presented late with stage IV and V ROP but now with timely screening correct diagnosis could have been made.

Lack of timely screening was the most important factor leading to advanced ROP as shown by Sanghi *et al.* also but false screening was also an important issue.[19] The maximum number of such cases was restricted to the first 2 years of duration of this study which suggests a lack of knowledge and

awareness among neonatologists and poor implementation of ROP screening program in the initial years.

The retrospective nature of this study has its own inherent drawbacks. The major limitation of this study is that the details of O_2 supplementation i.e., dose and duration of O_2 therapy were not studied. Maternal risk factors were also not studied in this study. Follow up of screening till maturity in cases of no ROP was highly variable in our records, due to lost to follow up. This is a limitation as some of these babies could have developed some form of ROP before complete maturity.

Conclusion

In conclusion, this study shows a quite high prevalence of severe ROP. Though low gestational age, low birth weight and late presentation are strongest predictors of severe ROP, but mean BW and mean GA of severe ROP and APROP cases were much higher than previous reports from India. Prevalence of APROP was very high which needs further investigation. Almost 7% of babies who developed severe ROP were outside the screening guidelines (>37 weeks and >2 kg birth weight). Presence of severe ROP in larger babies is probably an indicator that neonatal care needs to be improved further. This also warrants the need to set some basic minimum requirements for a NICU establishment, for example oxygen blender, without which NICU should not be allowed to function. It is very important to decrease the morbidity due to blindness in NICU graduates, not just for survival but a healthy survival of babies.

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Conflicts of interest

There are no conflicts of interest.

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