Indian Journal of Basic and Applied Medical Research; December 2019: Vol.-9, Issue- 1, P. 332 - 340

Original article

A study on the presumed etiological factors of Retinopathy of Prematurity in Kolkata, West Bengal

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Abstract:

Introduction: Retinopaty of prematurity is a vasoproliferative disorder of retina in premature babies which might give rise to total blindness .The aim of this study is to undertake a background analysis of the various presumed risk factors associated with this disorder .The study is based in a tertiary care centre in Kolkata, West Bengal.

Materials and Methods : The study has been undertaken as a part of the ROP screening programme held in collaboration with the Sick Neonatal Care Unit.The following parameters have been evaluated ,order of birth,birth weight, maternal morbidity, Gestational Age,Presenting age,H/O complications during pregnancy or childbirth,associated comorbidities of the baby and staging of the disease.

Results: 430 premature infants of both sexes were included for the study.Total number of ROP cases was found to be 104(24.2 %). The average birth weight of all the ROP cases was 1.15±0.43 Kgs. 66.67 % of the ELBW subjects were suffering from ROP. The mean gestational age of all the premature subjects examined diagnosed with ROP was 30.11 ±1.85 weeks. Most of the cases of ROP presented with stage 3 , with Stage 2 Zone 3 being the most common combination. Logistic regression analysis established that history of pulmonary complications in the newborn and Gestational Diabetes Mellitus are independent risk factors for ROP.

Conclusion: ROP has been given serious priority under WHO Vision 2020 programme.This project can be set as a reference Eastern Indian study for goal and target formulation in appropriate preventive and screening programmes like the WINROP algorithm.

Keywords: ROP, Etiology of ROP

Introduction

The disease called retrolental fibroplasia (RLF) by Terry[1] in the 1940s was defined as a progressive disorder seen exclusively in premature infants of low birth weight, characterized by fibrovascular proliferation behind the lens, resulting in severe visual handicap.The renewed wave of interest on this disorder swept across countries when the use of supplemental oxygen in closed incubators, came into frequent use,which helped to improve the survival of preterm infants, but also contributed to blindness.[2] Gradually as more studies were conducted on this disorder , now commonly referred to as Retinopathy of prematurity (ROP),several risk factors[3] were identified. A number of studies have been done in India as well as abroad but the epidemiological data of the Eastern part of our country is

inadequate.This research is an effort to assess the risk factors of Retinopathy of Prematurity as applied to a cohort of premature infants in a fully equipped neonatal care unit in Kolkata, West Bengal.

Aims &Objectives

To assess the risk factors of Retinopathy of Prematurity in premature infants in a Sick Neonatal Care Unit in a tertiary care hospital in Kolkata, West Bengal.

Materials and Methods

This was a prospective cohort study of preterm infants admitted in a tertiary neonatal intensive care unit from September 2017 to August 2018. The study has been undertaken as a part of the ROP screening programme held in collaboration with the Sick Neonatal Care Unit(SNCU), where all preterm and low birth weight babies have been examined to rule out ROP or its sequelae. The study included preterm infants meeting one of the following criteria:

(a) BW ≤ 1500 g or GA ≤ 32 weeks; or

(b) BW > 1500 g or GA from 32 to 37 weeks and any of the following risk factors: History of respiratory distress in the immediate postnatal period requiring ventilator support of any duration in a Sick neonatal care unit and History of Maternal Gestational Diabetes Mellitus defined as, (when any of the following plasma glucose values meet or exceed: Fasting: ≥ 5.1 mmol/L (92 mg/dL), 1-hour: ≥ 10.0 mmol/L (180 mg/dL), 2-hour: ≥ 8.5 mmol/L (153 mg/dL)7 with 75 g OGTT according to International Association of the Diabetes and Pregnancy Study Groups (IADPSG) guidelines)

The infants with external or internal organic defects in the eyes not suggestive of the sequelae of ROP were excluded from the study.

Fundoscopy was performed under mydriasis with one drop of 0.5% tropicamide eye drops combined with 1% phenylephrine eye drops instilled three times in each eye, with 15-minutes interval in between, before examination. Retinal examination was performed at bedside using a binocular indirect ophthalmoscope (Carl ZEISS Zsl-5010), a 20-diopter lens (Volk Optical Inc.,USA), a newborn eyelid speculum(Alfonso eye speculum Newborn, storz ophthalmic instruments)and a pediatric scleral depressor (Spaide Pediatric Scleral Depressors by Bausch & Lomb). The examination was conducted by one of the authors , an ophthalmologist with adequate experience in diagnosis and management of pediatric retinal diseases.

Each patient was classified according to the most advanced stage of ROP observed during follow-up assessment, considering the eye with more advanced disease, based on the International Classification of Retinopathy of Prematurity[4] Data collection was discontinued when retinal vascularization was complete, reaching extreme temporal periphery, or when ROP showed complete regression after treatment. After that, patients were referred for routine follow-up assessment with a pediatric ophthalmologist at 6 months of age. Patients discharged from the SNCU were scheduled for outpatient follow-up .

Study variables selected were,Birth Weight, Gestational Age , Sex, number of days on any oxygen therapy or on continuous positive airway pressure (CPAP) or mechanical ventilation and History of gestational Diabetes of mother as per International Association of the Diabetes and Pregnancy Study Groups (IADPSG) guidelines. Statistical calculations were performed using SPSS software version 22.0, and R software version 3.3.0 alingwith Microsoft Excel 2007 Normally distributed data were subjected to Descriptive statistics .

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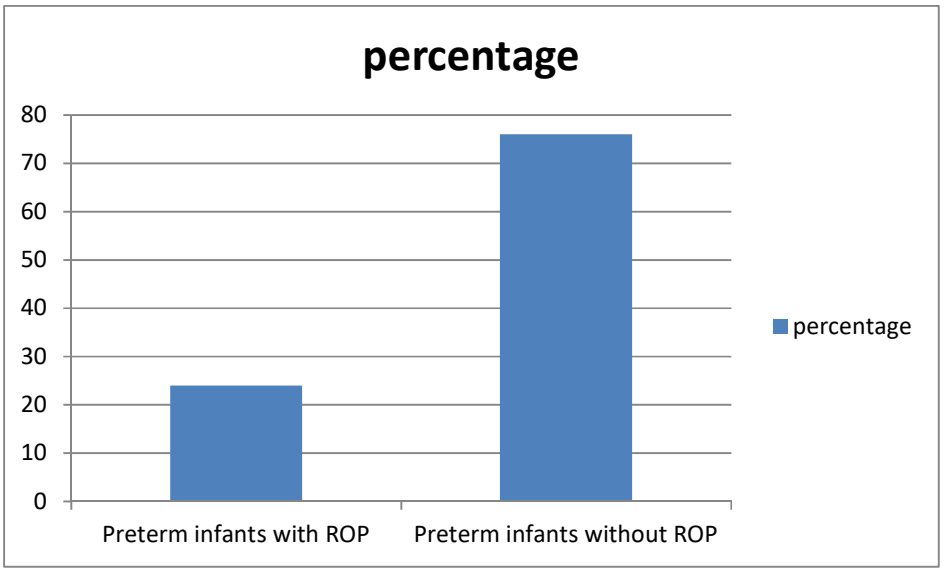
Categorical variables were reported as counts and percentages. Comparisonswere made between patients with and without ROP. Quantitative data were analyzed using the Student's t test for normally distributed variables. A logistic regression model was used to estimate the association between risk factors and development of ROP.

Results

430 premature infants of both sexes were included for the study.Total number of ROP cases were found to be 104(24.2 %).No sex dominance was noted.

Fig 1.Bar diagram sowing percentage of preterm infants with and without ROP in the study population.



The average birth weight of all the ROP cases was 1.15±0.43 Kgs.12% of the study population was having extremely low birth weight(ELBW)(less than 1000 grams).6% o the total no. of the ROP cases were found to ELBW.The maximum value of the birth weight that developed ROP was 2000 grams.66.67 % of the ELBW subjects were suffering from ROP,while 6% of the total ROP cases were weighing <1000 Grams(ELBW).35 % o these ELBW ROP cases were having stage 3 disease and 13 % of them had plus disease. The average birth weight of all the Non ROP cases was 1.66±0.51 Kgs.The t stat is significantly greater than the t critical one tail showing that the null hypothesis that the average birth weight of premature children with and without ROP are in the same range is hereby rejected with a high index of probability.p value with notation of e indicates highly statistically significant result, however homosdecasticity of the data cannot be assumed .

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t-Test: Two-Sample Assuming Equal Variances		
	ROP	*NON ROP*
Mean	1.670203	1.188435
Variance	0.23243	0.079436
Pooled Variance	0.197	
Hypothesized Mean Difference	0	
Df	95	
t Stat	4.546723	
P(T<=t) one-tail	8.03e-06	
t Critical one-tail	1.661052	
P(T<=t) two-tail	1.61e-05	
t Critical two-tail	1.985251	

The mean gestational age of all the premature subjects examined diagnosed with ROP was 30.11 ±1.85 weeks with a standard error o 0.512. 34 weeks was the largest value of gestational age found in our study.The ROP cases occurred with highest frequency at 34 weeks gestation in our study population.The t test shows the test statistic is more extreme than the critical value, so the null hypothesis is rejected in favor of the alternative hypothesis with signicant statistical significance.

t-Test: Two-Sample Assuming Equal Variances		
	ROP	*Non ROP*
Mean	30.77273	33.87838
Variance	6.088745	10.35487
Pooled Variance	9.401798	
Hypothesized Mean Difference	0	
df	94	
t Stat	-4.17099	
P(T<=t) one-tail	3.38E-05	
t Critical one-tail	1.661226	
P(T<=t) two-tail	6.75E-05	
t Critical two-tail	1.985523	

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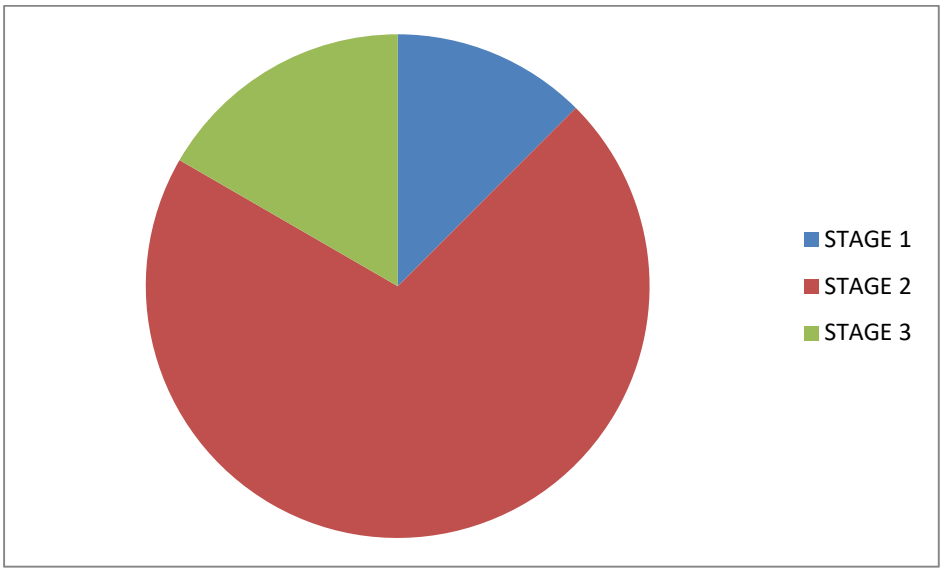
Most of the cases of ROP presented with stage 3 , with Stage 2 Zone 3 being the most common combination.

Fig 2:Piechart showing various stages of ROP in the study population.



Data was subjected to univariate analysis of the two other common risk factors for ROP i.e. History of antenatal maternal diabetes mellitus and intrarnatal or immediate postnatal pulmonary complications in the neonate warranting ventilator support .In either of the two scenarios univariate analysis yielded a high odds ratio with statistical significance.

Table 1 briely outlines the statistical analysis of the Risk factors of ROP as evaluated in our study

Risk Factors	Retinopathy of Prematurity		
	OR	95% CI	P value
Birth wt.<1500 gms	10.67	3.73-30.45	<0.0001
Pulmonary Disease	6.22	2.29-16.93	0.0003
Maternal Diabetes Mellitus	8.93	2.84-28.14	0.0002
Gest. Age<32 wks	3.12	1.21-8.05	0.02

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Using multiple regression analysis for the above four variables the following results were obtained:

Regression Statistics					
Multiple R	0.59307209				
R Square	0.351734504				
Adjusted R Square	0.323852117				
Standard Error	0.355421276				
Observations	430				
ANOVA					
	df	*SS*	*MS*	*F*	*Significance F*
Regression	4	6.374291	1.593573	12.61494	3.06162E-08
Residual	93	11.74816	0.126324		

The Multiple regression analysis is thus statistically quite significant as the probability of the said regression model is much less than 0.05.

Discussion

A number of studies have been conducted in India and abroad regarding the risk factors of Retinopathy of Prematurity. However data in this part of the country is insignificant.Corroborative epidemiological data is also lacking. Vasavada D et al [5] in their study in Western India noted Out of 280 babies screened, any-ROP was seen 54 babies(19.28%).A comparable percentage (24.2% of the 430 infants) was found in our case. Ahuja et[6] al did similar study in the perspective of Southern India.. In their case a total of 325 infants were screened. ROP was identified in 210 eyes of 106 (32.6%) babies with severe ROP (stage ≥3 ROP) occurring in 14 (13.2%) babies.The overall incidence of ROP in India[7] is 27% Incidence of ROP in other parts of the world are as follows, in Brazil (25.5%) [8],Norway (33%) [9], Oman (34%) [10], Finland (27.3%) [11], and Singapore (29.3%) [12] .The rising rates of ROP in all parts of the world are indicative of better survival rate of premature infants where neonatal care is sufficient to save the babies' lives but not enough to prevent hyperoxic damage to the premature retina and an increased rate of the aggressive posterior form of the disease.

Almost all the available literature suggest that gestattinal age is the most common risk factor associate with the condition. lower the birthweight, the more severe is the loss of factors usually provided by the intrauterine environment for which the immature fetus is unable to take over production. The Vermont Oxford Network database[13], which collects data from more than 1000 NICUs worldwide, estimated in 2010 an incidence of 33.2% of ROP in neonates with BW < 1500 g.In our study also a value as high as 66.67 % of the ELBW subjects were suffering from ROP.35 % o these ELBW ROP cases were having stage 3 disease and 13 % of them had plus disease.According to Ahuja et al in the South Indian study, Low BW (LBW) was the only significant risk factor for ROP on multivariate logistic regression analysis. The mean BW was 1285 and 1452 g for babies with and

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without ROP, respectively.In our case The average birth weight of all the ROP cases was 1150 grams and that for the non ROP cases was 1560 grams.In a recent Brazilian study[14] 48% of the ROP cases were having birth weight <1000 grams. In the present study scenario, 6 % of the total cases were having ELBW,suggesting less chances of survival and progression to ROP in these circumstances. When very preterm infants are born with a weight appropriate for gestational age, birth weight is likely to be a proxy for gestational age and not an independent risk factor.[15]

As noted in all studies this study also shows prematurity as an independent risk factor.A point of note in this regard is that depending on the extent of survival of the extremely premature infants the average age of the ROP case tend to vary in various parts of the world. The mean gestational age of all the premature subjects examined diagnosed with ROP was 30.11 ±1.85 weeks in our study wich corroborates well with the Brazilian study by Freitas et al.The cut off gestational age for prematurity is usually taken as 32weeks,but in our case the cases of ROP occurred most frequently in the 34 week bracket as most of these were coupled with LBW or ELBW.

Supplemental oxygen given to premature infants with respiratory distress can lead to oxidative damage to the developing retina. Hyperoxia induced new vessels occurrs at the junction between vascularised and avascular retina in the mid periphery.[16] The present study clearly shows the detrimental effect of supplemental oxygen therapy given to premature sick neonates with pulmonary complications. Sick neonates with pulmonary complications in our study developing ROP was having an odds ratio of 6.22 which is on the higher side when compared the odds ratio for similar event in the study conducted by Freitas et al(OR of 2.49) Although no individual study has been conclusive as to the best SpO2 target, targets should be different in

different stages of development and in the different phases of retinopathy of prematurity. Strict management of oxygen to minimise alternating hypoxia and hyperoxia and avoidance of undesired high oxygen saturations in phase 1(hyperoxia –vasocessation phase) seem to be the most promising strategies to prevent retinopathy of prematurity, although this outcome has to be balanced against the effect on other morbidities such as cerebral palsy and death.[17]

Authors have been noted to have conflicting opinions regarding the association between maternal gestational diabetes mellitus and the incidence of ROP.In the study conducted by Tunay ZO et al[18], Maternal diabetes was shown to be an independent risk factor for ROP (OR with 95% CI: 25.040 [12.728-49.264] and P < .001 .The study conducted by us also concludes that Maternal Diabetes as an independent risk factor for ROP but with a lower Odds Ratio(OR 8.93 95%CI 2.84-28.14 and p=0.0002.The studies undertaken by Kavurt S[19] and Yu XD[20] however are of the opinion that maternal Diabetes has no correlation with the incidence of ROP. The levels IGF-1 rise significantly during the 3rd trimester of pregnancy, and it controls VEGF mediated vascular growth in the retina. However, IGF-1 levels fall rapidly after preterm birth, and prolonged period of low IGF-1 in preterm children have been reported to be associated with development of ROP.Gestational diabetes is known to cause an elevation of maternal IGF 1 (responsible for macrosomia)and IGF2 but the effect of maternal diabetes on Fetal IGF is still under evaluation. We are of the opinion that gestational diabetes might hamper the IGF-VEGF axis in the preterm neonate resulting in development of ROP.

The multiple regression analysis with the above mentioned independent variables have been found to have a R^2 value of 35%(R square 0.351 with standard error of 0.355). It suggests that the risk factors of this study have got a

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35 % predictive value regarding the outcome of ROP in the concerned neonate.This is the basic limitation of the present study as it clearly indicates that, several other independent risk factors have not been considered which could have yielded a higher R square and a higher predictive statistical value.However, that these variables are independent risk factors affecting the outcome of the depenent variable, ROP ,in this case have been established beyond doubt from a statistical point of view.

Conclusion

As sufficient epidemiological data pertaining to the incidence of ROP in West Bengal or the Eastern part of India is evidently lacking, this project aims to fill in the lacunae.This study might guide us in future ,if attempts are made to valdate the WINROP [21]algorithm in this part of the country as a powerful screening tool for ROP.This study also validates the claim that maternal diabetes Mellitus is an independent risk actor or ROP.A future study considering the other independent risk factors of ROP should also be undertaken in the coming days to prevent the newborns from the menace of this potentially disease threatening condition.

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