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Retinopathy of Prematurity: Prevalence, risk factors and co-morbidities

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Abstract: *Retinopathy of prematurity (ROP) is a disorder of retinal vasculature, characterized mainly by abnormal development of retinal vasculature and is an important and preventable cause of childhood blindness[1]. It usually affects premature babies who are exposed to certain risk factors like : low gestational age, low birth weight and prolonged exposure to supplementary oxygen after delivery[2] to which it is found to be associated with. Recent advancements in neonatal care have led to an increase in the survival of low birth weight and premature infants[3], resulting in a rise of ROP incidence[4,5]. This research aims to find out various risk factors and associated comorbidities with ROP.*

Keywords: *Retinopathy of Prematurity, gestational age, childhood blindness, low birth weight, sepsis, oxygen therapy, apnea, blood transfusion.*

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I. Introduction

Terry first described ROP in 1942[6]as retrolental fibroplasia, and sooner it became the primary cause of childhood blindness throughout the developed world[7]. It is estimated that ROP causes about 50,000 cases of childhood blindness in the world every year[8].In India alone,500 children are estimated to become blind from ROP every year[9].

Earlier ROP was found to be associated mainly with oxygen therapy. However later it was also reported in many cases without oxygen therapy also and it was found that even after oxygen therapy, not all premature infants developed ROP. Later, it was found that many factors are responsible for causing ROP but these three factors were found to be very strongly associated with ROP: low gestational age, low birth weight and prolonged exposure to supplementary oxygen after delivery[2].Other putative risk factors include mechanical ventilation, sepsis, intraventricular hemorrhage, surfactant therapy, apnea and anemia. Early diagnosis of ROP and the institution of appropriate treatment prevent blindness and offer child a better overall development.Retinal vascularization starts at optic nerve head at 16 weeks of gestation then progresses to the periphery. Vascularization is almost completed by the term.Inside the uterus, the fetus is in a hypoxic state in contrast to after birth. In premature infants, the growth of retinal vessels is stimulated by vascular endothelial growth factor (VEGF). After birth, the immature retina is usually exposed to hyperoxia, which inhibits vascular endothelial growth factor (VEGF) and thus vessels stop growing. After some time, the avascular retina becomes ischemic and stimulates VEGF which leads to arterial-venous shunts and finally uncontrolled neovascularization occurs.

II. Material And Method

We are conducting a prospective cross sectional study at JN Medical College A.M.U. Aligarh, after taking ethical clearance from institutional Ethical Committee of the College.In this study we are trying to find out the prevalence and risk factors of ROP, we are also looking for co morbidities which are frequently associated with ROP. ROP screening of all premature babies who are admitted to NICU of the same college over a period of 18 months will be done after taking consent from their parents.

Brief clinical history will be taken including important gestational and perinatal events, torch light examination will be done, then patients will be examined after dilatation through indirect ophthalmoscope and findings will be recorded on a predesigned proforma. Further ROP staging and management will be done as required.

The ultimate aim of screening is to reduce the incidence of ROP, prompt case detection and to provide optimal treatment thereby reducing the severity and overall burden of childhood blindness. Screening guidelines differ for different countries depending upon incidence and prevalence of ROP and socioeconomic status.**Gupta et al (2004)**[10] in their study concluded that indirect ophthalmoscopy should be performed at 4 weeks of post natal age in all preterm babies with birth weight ≤ 1500 gram, and it should be intensified in the presence of risk factors like oxygen administration, apnea and septicemia.

ROP screening guidelines for India[11]
• Birth weight <1700 gram
• Gestational age at birth <34–35 weeks
• Exposed to oxygen >30 days
We screen all eligible babies at 31 weeks postmenstrual age or 4 weeks chronologic age, whichever is later.[12]

Table 4. Timing of the Initial Eye Examination Designed to Detect at Least 99% of Serious ROP*

Gestational Age at Birth, wk	Age at Initial Examination, wk	
	Postmenstrual	Chronologic
22†	31	9
23†	31	8
24	31	7
25	31	6
26	31	5
27	31	4
28	32	4
29	33	4
30	34	4
31	35	4
32	36	4

*ROP indicates retinopathy of prematurity.
†This guideline should be considered tentative rather than evidence based for 22- to 23-week infants owing to the small number of survivors in these gestational age categories.

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III. Result And Discussion

Following are some risk factors leading to the development of Retinopathy of prematurity:

Gestational Age at birth

As it is a disease of immature retina its occurrence is inversely related to gestational age. More premature the infant, the more likely the disease is to develop[13]. There exists a significant relationship between ROP and gestational age[14–16]. Median age of onset of ROP was found to be 35 weeks postmenstrual age[17]. **Rao et al (2013)**[18] conducted a study in Karnataka, India and found that gestational age at birth between 31-32 weeks is anindependent risk factors for ROP.

Birth weight

There exists a significant relationship between ROP and birth weight[14]. It is much more common among VLBW[19] (<1500 gram) and ELBW[20] (<1000 gram) babies. A study was done in Singapore by **Shah et al *(2005)***[17] in which they found that the incidence of ROP among VLBW infants was 29.2% and was found to be strongly associated with smaller, more sicker and immature infants.**Sood et al (2012)**[16]in their study found low birth weight as independent risk factors for ROP.

Oxygen Therapy

Earlier oxygen therapy was considered as the only risk factor for development of ROP. However later it was also reported in many cases without oxygen therapy also and it was found that even after oxygen therapy, not all premature infants developed ROP. But still a consistent and significant relationship between ROP and oxygen therapy has been established[2].Judicious use of ventilation and oxygen therapy may reduce the incidence

and severity of ROP[17].Wright et al concluded in his study that maintaining SpO2 between 83%-93% in immediate postgestation life along with strict control of oxygen fluctuations, ROP incidence and its severity can be reduced[21].

Apnea

Its contribution in the development of ROP is still controversial**. Le *et al*** found it to be a significant risk factor for ROP in their study conducted in Hyderabad in 2016[22] while **Alizadeh*et al*** in their study in Iran found it not to be a significant risk factor for ROP[15].

Sepsis

In many studies sepsis has been proved as a significant risk factor for development of ROP[19,22,23].

Blood transfusion

Blood transfusion and anemia increases the risk for development of ROP. Its relationship with ROP is still debatable. **Hakeem *et al*** in their study found a significant relationship between ROP and blood transfusion[23]. But **Alizadeh*et al*** reported that blood transfusion is not significantly associated with ROP[15].

Patent DuctusArteriosus and Respiratory Distress Syndrome

Their contribution to ROP is still not well established. In some studies they are found to be independently associated with ROP[20] while in other an insignificant relationship was found[23].

Many studies have been performed across the world to find incidence, prevalence and other risk factors associated with ROP. Results of some of the studies have been mentioned below:

Kim et al (2004)[24] conducted a study at Asan Medical Centre, Seoul, Korea, to investigate the postnatal risk factors of retinopathy of prematurity (ROP) and found gestational age ≤28 weeks and birthweight ≤1000 gram, ventilator care for ≥48 hours, apnea, and surfactant therapy as significant risk factors for development of ROP. They also found thatapnea may not only increase the risk of developing ROP, but may also worsen pre-existing ROP.**Shah et al(2005)**[17] conducted a study in Singapore and concluded that the incidence of ROP among VLBW infants was 29.2% and was found to be strongly associated with smaller, more immature and sicker infants. The main risk factors for development of ROP reported were extremely low birth weight (BW <1000 gram), extreme prematurity (GA <30 weeks), severe hyaline membrane disease with longer duration of mechanical ventilation and supplemental oxygen therapy. **Darlow et al (2005)**[25]in their study tried to find out prenatal and perinatal risk factors for the development of severe ROP and they found degree of immaturity, intrauterine growth restriction, and male gender as contributory factors for development of severe ROP.**Akkoyun et al (2006)**[26]conducted a study to evaluate the risk factors in the development of mild and severe Retinopathy of Prematurity and found birth weight and respiratory distress syndrome as independent risk factors for the development of mild ROP and birth weight in the development of severe ROP.**Kumar et al (2011)**[20]conducted another study to evaluate the risk factors predisposing to severe retinopathy of prematurity (ROP) among preterm low bith weight neonates in NICU of a tertiary centre and found Respiratory distress syndrome, PDA and meningitis to be associated with severe ROP**.**Another study was conducted by **Hakeem et al (2012)**[23] at NICU of Al Minia University hospital.Univariate analysis showed that there was a significant relationship between the occurrence of ROP and gestational age (P = 0.000), sepsis (P = 0.004), oxygen therapy (P = 0.018), and frequency of blood transfusions (P = 0.030).**Taquiet al** (2012)[27] in theirs study conducted at NICU of a tertiary care hospital in Pakistan, analyzed 68 neonates(birth weight< or =1500 gram and gestational age < or =32 weeks) and found that 32.4% neonates developed ROP (inclusive of all statges) and 20.6% developed threshold disease,and also found low gestational age, sepsis and respiratory distress syndrome as independent risk factors for ROP development. Another study was conducted by **Kavurt et al(2014)**[19]to evaluate the incidence, risk factors and severity of retinopathy of prematurity in neonatal intensive care unit and to evaluate its relationship with gestational age. They analyzed risk factors for ROP in patients ≤32 weeks GA or ≤1500gram BW. In the logistic regression model, presence of sepsis and being small for gestational age (SGA) were found to be independent risk factors for severe ROP. **Alizadeh et al(2015)**[15]in their cross-sectional retrospective study at Amiralmomenin Eye Hospital, Iran, found low birth weight, low gestational age, oxygen therapy, phototherapy, blood transfusion and apnea as possible risk factors for ROP. After logistic regression analysis, only low GA and low BW were independently associated with the condition. According to them risk factors for ROP including phototherapy, blood transfusion, apnea and intraventricular hemorrhage, which were in agreement with previous studies, were not found to be significantly associated with ROP after multivariate regression analysis. **Le et al (2016)**[22]found the incidence of ROP in their study conducted at NICU of a tertiary care hospital located in Hyderabad as 2.3%.They also concluded that the most prevalent postnatal risk factors among patients with ROP were RDS and use of oxygen therapy. 58% of patients with ROP experienced RDS and 71% needed oxygen therapy. Other significant postnatal risk factors noted were presence of sepsis (33%), transient tachypnea of the newborn (20%), apnea of prematurity (20%), patent ductusarteriosus (17%), hypoglycemia (15%), and neonatal seizures (6%).

TREATMENT

It is very important for an ophthalmologist to decide when to treat and when to observe the patient of ROP. Current treatment guidelines for ROP are based upon ET-ROP study[28].This study showed that early treatment of high risk prethreshold disease significantly reduces the unfavourable outcomes [29]. According to this study treatment should be given to any eye with:

Type 1 Retinopathy of prematurity:

- Zone I – having any stage ROP with plus disease
- Zone I – having stage 3 ROP without plus disease
- Zone II – having stage 2 or 3 ROP with plus disease

ET-ROP also indicates that continued serial examinations should be considered for eyes with:

Type 2 Retinopathy of Prematurity:

- Zone I- having stage 1 or 2 without plus disease
- Zone II- having stage 3 without plus disease

Treatment should be considered for an eye with Type 2 ROP when progression to type 1 status or threshold ROP occurs.

Sometimes terms like 'threshold' and 'prethreshold' are also used:

Threshold ROP – ROP with at least five contiguous or eight cumulative clock hours of stage 3 ROP in zones I and II in presence of plus disease.

Prethreshold ROP- ROP which has a high likelihood of progressing to threshold ROP.

Threshold ROP and more severe forms of prethreshold ROP, require treatment and are incorporated in the type 1 ROP category[30].

Earlier cryotherapy was performed for treating ROP but during late 1990s laser ablation gained acceptance as an alternative to cryotherapy.In general, it was found that the laser therapy, using the binocular laser indirect ophthalmoscope delivery system is technically easier than cryotherapy and creates fewer postoperative sequelae, such as inflammation and swelling[31].In a study it was found thatearly treatment of high-risk prethreshold ROP using peripheral retinal ablation of the avascular retina significantly reduces unfavorable outcomes to a clinically important degree[24]. Furthermore, the outcomes of treatment of threshold disease in zone I and posterior zone II were superior to cryotherapy, and at least equivalent to cryotherapy results for zone II disease[32].

Recently anti-VEGF agents, mainly intravitrealbevacizumab, is emerging as a treatment for acute retinopathy of prematurity[33]. A prospective multicenteric study was done in which 150 infants with bilateral stage 3+ disease in zone I or posterior zone II were randomized to intravitrealbevacizumab (0.625 mg) versus conventional laser treatment. The result showed that infants who were treated with bevacizumab for stage 3+ disease in zone I had significantly fewer disease recurrences and better structural outcomes at 54 weeks postmenstrual age, although there was no difference for infants with ROP in posterior zone II[34].It was also found that development of peripheral retinal vessels continued even after treatment with intravitrealbevacizumab, but permanent destruction of peripheral retina occurs after conventional laser. Another study by **Zhang G *et al***compared intravitrealRanibizumab (IVR) with laser therapy for Zone II ROP requiring treatment, they concluded that although IVR appears to regress ROP to certain levels and continue to promote the vascularization of peripheral retinal vessels, a substantial proportion of infants developed recurrence of ROP after a single-dose IVR. Therefore, IVR is not recommended as a single-dose monotherapy for Zone II ROP which requires treatment.[35]

The outcome of surgeries for treatment of end stage ROP is not very good. Hence timely intervention in the form of laser treatment or anti-VEGF must be given. There is need to increase the awareness and to diagnose cases earlier so that they can be treated on time.

Vitamin E was considered as a potential agent to prevent ROP due to its antioxidant properties[36].Even after many randomized and controlled trials the efficacy of prophylactic vitamin E supplementation in either reducing the incidence or the severity of ROP is still controversial[37].

IV. Conclusion

1. Early detection and prompt treatment is the key to guard against this very important cause of childhood blindness.
2. Proper NICU andtertiary level care is important. Hence referral of such premature babies to advanced carecentre is a must.
3. We require lot of trained retinal surgeons in ROP care as the magnitude of the problem is ever increasing.
4. Co morbidities have an important role in ROP management. Hence an ophthalmologist has to be a bit of neonatologist too. He should know and discuss various parameters on the NICU monitor with the team of doctors and even nurses to provide in toto care of the premature baby..

5. There isneed to increase the awareness of the disease and to make sure these babies are diagnosed and treated on time to insure good visual prognosis in such cases.
6. Also there is need of much more studies to be done to find many other risk factors and co morbidities associated with ROP.

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