Research Article

Screening Guidelines to Reduce Childhood Blindness Due to Retinopathy of Prematurity

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Abstract

Objectives: To assess the severity of retinopathy of prematurity (ROP) in relation to its established risk factors and to evaluate the impact of current treatment approaches.

Methods: This study is a comprehensive review of the available literature. The severity of ROP is classified according to the International Classification of Retinopathy of Prematurity (ICROP3).

Results: Increased awareness and education about ROP, along with timely screening, play a crucial role in reducing the risk of childhood blindness. Emphasis is also placed on addressing the medico-legal implications associated with delayed diagnosis and treatment.

Conclusion: "Prevention is better than cure"—by identifying and managing risk factors early, and implementing effective screening programs, we can significantly reduce the burden of blindness caused by ROP in society

Keywords: Childhood blindness, Premature infants, ROP, Early screening.

Introduction

Retinopathy of prematurity (ROP) is a disorder of the retina featuring abnormal proliferation of developing blood vessels.[1] The term' Retinopathy of Prematurity' was first introduced in the 1950s by Philip Heath.[2] ROP is a preventable cause of neonatal blindness and carries significant clinical and medico-legal implications for ophthalmologists and neonatologists alike.

Epidemiology:

As of 2024, ROP remains a significant cause of preventable childhood blindness, particularly in developing countries like India. Here's an overview of the current epidemiological landscape:

Global Incidence:

Around 15 million babies were born prematurely worldwide. This represents about 10% of all live births.[3] The global prevalence of ROP was estimated at 31.9%, with 7.5% of cases being severe.[4]

Incidence and Severity in India:

A 2020 study in *The Lancet* reported that India contributed around 3.02 million preterm births, accounting for more than 20% of preterm births worldwide.[5] Refer to Table 1 for the summary.

ROP in North India: Insights

- Incidence and Risk Factors: A 2023 study in Uttar Pradesh reported that 19.7% of preterm infants developed ROP (6). The main risk factors included lower gestational age, sepsis, oxygen therapy, and blood transfusions.[6]
- Trends Over Time: A five-year study from a tertiary care institute in North India revealed an overall ROP incidence of 32.3%, with a rising trend in aggressive posterior ROP (APROP) cases, from 16% in 2013 to 28% in 2017.[7]

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Table 1: shows the summary of ROP incidence

Region	*ROP Incidence (%)*	*Severe ROP (%)*	*Key Risk Factors*	*Screening Challenges*
Global	31.9	7.5	Prematurity, low birth weight, and oxygen use	Variable protocols, resource limitations
Uttar Pradesh (India)(6)	19.7	Not specified	Lower GA, sepsis, oxygen therapy, and transfusions	Shortage of trained ophthalmologists
North India (7)	32.3	Not specified	Outborn status, delayed screening	Delayed presentations, APROP increase

Risk factors in ROP

Premature birth before 34 weeks of gestation and low birth weight under 2000 g are significant risk factors for ROP.[8]

Other risk factors:

- Excessive usage of oxygen
- Early light exposure
- Anemia
- Thrombocytopenia
- Neonatal sepsis
- Respiratory distress syndrome
- Multiple birth (twins/triplets, etc.)
- Maternal co-morbidities

(TORCH Infection, Hypertension, Gestational Diabetes)

- Intraventricular hemorrhage.[8,9]

It is a treatable disease, but in time, screening of the babies is a must. Early recognition of the disorder leads to early detection, which can reduce visually impaired offspring.

The main guidelines for screening in India are

- Indian Association of Pediatrics (IAP).[8]
- Rastriya Bal Suraksha Karyakaram (RBSK).[9]
- National Neonatology Forum (NNF).[10]

Screen whom

- At 4 weeks of age, this applies to all premature and at-risk newborns.
- Infants with birth weight ≤2000 g.
- Infants with higher gestational age or birth weight but with risk factors such as sepsis, oxygen therapy, or blood transfusions.[8,9]

Screen when

The first examination for ROP

- At 4 weeks for all premature and at-risk neonates
- At 2–3 weeks, if the neonate is <28 weeks of gestation or has birth weight ≤1,200 g, or if gestation at birth is not confirmed.[8,9]

Screening complete

- ROP screening can be stopped by the time complete vascularization is observed (By 40–44 weeks of gestation, the vascularization is completed, but if ROP is present, screening has to continue weekly or bi-weekly).[8]

Screen by whom:

- Trained ophthalmologists should conduct the screening.
- In telescreening setups, trained paramedical staff can capture retinal images for evaluation.

Screen where

- Neonatal intensive care units (NICUs) or specialized ophthalmic clinics with sterile or clean environments suitable for examination of infants.

Pathophysiology

Normal circumstances (Intrauterine environment)

- Retinal blood vessel formation begins as early as 14–15 weeks of gestation.
- These vessels emerge from the optic disc and extend outward toward the peripheral retina.
- The process of angiogenesis is largely driven by hypoxia-inducible factor-1alpha (HIF-1α), which regulates the production of vascular endothelial growth factor (VEGF) and placental growth factor (PlGF).
- By approximately 36th week of gestation, the nasal retina is fully vascularized.
- The temporal retina completes vascular development around 40 weeks of gestation.[11]

When does ROP develop?

The development of ROP is typically described in two stages, as proposed by Ashton's two-phase hypothesis (Figure 1):

Phase I – Vascular Growth Arrest (Vaso-obliteration)

- When preterm infants are exposed to high levels of oxygen after birth, along with insufficient nutritional support, there is a suppression of essential growth factors like insulin-like growth factor-1 (IGF-1).
- This disruption hinders the normal maturation of retinal vasculature, causing the growth of retinal vessels to temporarily halt or regress.

Phase II – Abnormal Vessel Proliferation (Vaso-proliferation)

- As the infant grows, the immature retina continues to develop and demands more oxygen, leading to a hypoxic environment in avascular regions.
- In response, the retina increases production of IGF-1, which enhances the activity of VEGF, triggering a renewed but disorganized growth of blood vessels.

- These newly formed vessels are fragile, prone to leakage, and grow into the vitreous instead of the retinal plane.
- The resulting complications can include:
  - Retinal hemorrhage
  - Fibrous tissue formation
  - Retinal scarring
- Over time, these changes can cause tractional retinal detachment due to contraction of the fibrovascular membranes.[11-13]

Classification of ROP

To standardize the evaluation and management of ROP, a comprehensive system known as the International Classification of Retinopathy of Prematurity, Third Edition (ICROP3)(14) has been established. This most recent update includes several refinements:

- Introduction of Posterior Zone II
- Definition of Notch
- Sub-classification of Stage 5 ROP
- Revised criteria for Aggressive ROP (A-ROP)

The classification is based on several parameters that describe the location, severity, and extent of the disease.

Anatomical Location (Zones)

The retina is divided into three concentric zones centered on the optic nerve:

- Zone I: A circle with a radius twice the distance from the optic disc to the macula.
- Zone II: Extends from the edge of Zone I to the nasal ora serrata.

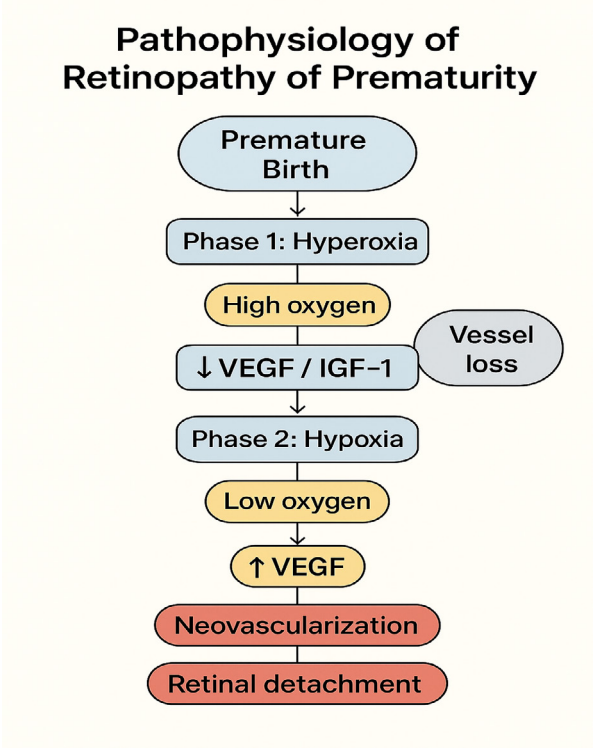

Figure 1: Pathophysiology of ROP

- Posterior Zone II: A newer term describing a region within Zone II, measuring a radius equal to two disc diameters from the margin of Zone I.
- Zone III: The crescent-shaped peripheral area of the retina beyond Zone II.

Notch refers to a situation where ROP appears to extend into more than one zone. The location of the lesion is then determined by the most posterior extent of the disease.

Stages of Severity

ROP is graded by the degree of abnormal retinal vascular development:

- Stage 1 – Demarcation Line: A thin, flat, white line separating vascular from avascular retina.
- Stage 2 – Ridge: The demarcation line becomes elevated and wider, often appearing pink or white. Small protrusions of neovascular tissue called "popcorn lesions" may be seen posterior to the ridge.
- Stage 3 – Extraretinal Fibrovascular Proliferation: Abnormal new blood vessels extend from the ridge into the vitreous.
- Stage 4 – Partial Retinal Detachment:
  - 4A: Detachment does not involve the macula.
  - 4B: Detachment includes the macula.
- Stage 5 – Total Retinal Detachment:
  - 5A: The optic disc is still visible (open funnel configuration).
  - 5B: The optic disc is obscured due to fibrovascular tissue (closed funnel).
  - 5C: Advanced cases with anterior segment involvement, such as displaced lens, shallow anterior chamber, or corneal opacity.

Extent of Disease

The spread of ROP is described in clock hours, dividing the retina into twelve 30° sectors to specify the area of involvement.

Associated Vascular Changes

- Pre-Plus Disease: Indicates early signs of abnormal vascular dilation and tortuosity, but not severe enough for a diagnosis of plus disease.
- Plus Disease: Significant dilation and tortuosity of the posterior retinal vessels, particularly in the arterioles and venules.

Aggressive Retinopathy of Prematurity (A-ROP)

A-ROP is a severe and rapidly progressive form of the disease that does not follow the usual stage-wise development. It is characterized by prominent plus disease, flat neovascularization, and can occur in any zone, often requiring urgent intervention due to its intensity.[14]

Material And Method

This article is based on a review of the existing literature. The selection of patients largely depended on referrals and awareness generated by neonatologists, emphasizing the

recognition of ROP and its retinal effects. A comprehensive patient history was obtained, including assessment of known risk factors and detailed maternal gestational history, to ensure a thorough understanding of the available clinical data

Screen how

Screening was conducted by an ophthalmologist, with informed consent obtained from the parents or guardian. The following steps were followed:

- The anterior segment of the eye was examined, and pupillary reactions were assessed.
- Pupils were dilated using Tropicamide 0.5% combined with Phenylephrine 5%.
- Proparacaine 0.5% eye drops were instilled in both eyes to provide local anesthesia prior to examination.
- The infant was gently immobilized by secure holding to minimize movement.
- A sterile infant eye speculum was inserted, and lubricating eye drops were applied to protect the ocular surface.
- A complete fundus examination was performed using an indirect ophthalmoscope with a 20-diopter lens. A scleral indenter was used to evaluate the peripheral retina.
- The examiner first observed the red reflex (glow) and assessed media clarity, followed by a detailed evaluation of the posterior pole and retinal vessels (specifically noting signs of plus disease). Subsequently, the peripheral retina was systematically examined in all clock hours. Findings were documented and recorded.
- Follow-up examinations were scheduled for infants without complete retinal vascularization to monitor disease progression or regression.

Multiple screening visits were often necessary to assess changes in retinal vascular development over time.

The early treatment for retinopathy of prematurity (ETROP) trial[15] introduced a classification system that helps determine whether an infant needs immediate treatment or just monitoring. This system divides ROP into two main categories:

Type 1 ROP (Requires treatment)

Infants classified under Type 1 ROP are at a higher risk of progressing to severe retinal damage and need early intervention. Treatment is recommended if any of the following conditions are present:

- Any stage of ROP in Zone I accompanied by plus disease
- Stage 3 ROP in Zone I even without plus disease
- Stage 2 or 3 ROP in Zone II with plus disease

In addition, aggressive ROP (A-ROP) in any retinal zone should also be treated promptly because of its rapid and severe progression.

Type 2 ROP (Requires Careful Observation)

Type 2 ROP has a lower immediate risk of progression but needs regular follow-up exams to monitor any worsening. Infants fall under this category if they meet the following:

- Stage 1 or 2 ROP in Zone I without plus disease.
- Stage 3 ROP in Zone II without plus disease.[15]

This approach allows healthcare providers to focus treatment on infants who are most at risk while avoiding unnecessary interventions in milder case.

ROP can be managed through three primary treatment approaches, each tailored to the stage and severity of the disease:

- Laser photocoagulation
- Intravitreal anti-VEGF therapy
- Vitreo-retinal surgery

Laser Photocoagulation

The goal of treatment is to halt disease progression by promoting the regression of abnormal blood vessels. Laser photocoagulation works by destroying the peripheral, non-vascularized retina. This creates scar tissue that transforms hypoxic retinal zones into anoxic areas, reducing the stimulus for vascular endothelial growth factor (VEGF) production. However, this procedure comes at the cost of losing some peripheral retinal function, which may narrow the visual field.[8]

Intravitreal Anti-VEGF Therapy

For cases involving posterior ROP, intravitreal injection of anti-VEGF agents offers an effective alternative. Multiple clinical trials have demonstrated the effectiveness of different anti-VEGF drugs:

- BEAT-ROP study (2011) evaluated Bevacizumab.[16]
- CARE-ROP trial (2018) focused on Ranibizumab.[17]
- RAINBOW study (2019) assessed Ranibizumab further.[18]
- BUTTERFLEYE trial (2023) investigated Aflibercept.[19]

These agents work by inhibiting VEGF, thereby reducing abnormal vessel proliferation in the retina

Vitreo-retinal Surgery

Surgical intervention is reserved for advanced stages of ROP, particularly when retinal detachment has occurred and other treatments have failed. Surgery aims to repair retinal structure and preserve any remaining vision.

Result

Reducing Childhood Blindness through Timely ROP Screening

Early detection and intervention are pivotal in preventing vision loss due to ROP. Timely screening of at-risk infants—particularly those born prematurely or with low birth weight—enables the identification of ROP in its nascent stages, allowing for prompt treatment that can halt disease progression and preserve vision. Implementing standardized screening protocols in neonatal care units has been shown to significantly decrease the incidence of ROP-related blindness, thereby alleviating the long-term societal and economic burdens associated with visual impairment.[20]

Enhancing Awareness and Education among Healthcare Professionals

A critical component in combating ROP is the education of healthcare providers about the condition's risk factors, the

significance of early screening, and the available treatment modalities. Initiatives such as ROP Awareness Week aim to disseminate knowledge and best practices among pediatricians and ophthalmologists, ensuring a cohesive and informed approach to ROP management. By fostering a well-informed medical community, these efforts contribute to improved patient outcomes and the prevention of avoidable blindness.

Addressing Medico-Legal Implications of ROP Management

The medico-legal landscape surrounding ROP underscores the necessity for diligent screening and documentation. Delayed or missed diagnosis can lead to legal actions against healthcare providers, emphasizing the importance of adhering to established screening guidelines and maintaining thorough records. Understanding the legal responsibilities and potential ramifications associated with ROP care is essential for medical professionals to mitigate risks and uphold the highest standards of patient care.

Discussion

Prevention remains the cornerstone of ROP treatment. To address the growing challenge of ROP, several new strategies and technological advancements have been introduced.

ROP Screening Algorithms

In today's clinical setting, accurately identifying infants at risk for developing ROP is critical. An important innovation is the creation of online tools for risk assessment, with the WINROP algorithm emerging as one of the most widely adopted. This algorithm uses serial measurements of an infant's postnatal weight gain and serum IGF-1 levels from birth up to a postmenstrual age of 36 weeks to predict the likelihood of developing ROP and guide timely screening decisions.[21]

Tele-Screening

In many developing countries, access to timely ROP screening remains limited due to a shortage of trained ophthalmologists and inadequate infrastructure. To overcome these challenges, telemedicine-based screening programs have been implemented. High-quality fundus images can be captured using RetCam imaging systems or smartphone-based fundus photography, which are then remotely reviewed by specialists.[22]

In India, telemedicine programs like Aravind Eye Hospital's ROPE-SOS.[23] and the KIDROP (Karnataka Internet-Assisted Diagnosis of ROP).[24] initiative have proven effective in broadening access to screening services. Additionally, international tele-screening models like TeleROP SS and SUNDROP (Stanford University Network for Diagnosis of ROP) have contributed to remote diagnosis efforts.[25]

Artificial Intelligence in ROP Diagnosis

Artificial Intelligence (AI) is an emerging force transforming medical diagnostics globally, and ROP is no exception. Several research projects are investigating AI-driven tools for automated ROP detection and classification. One prominent example is i-ROP DL (deep learning-based AI system), which is designed to enhance diagnostic accuracy and assist clinicians in identifying disease severity.[26]

Alongside improvements in screening and diagnosis, ongoing research continues to explore novel therapeutic options aimed at improving outcomes in infants with ROP.[26]

In summary, early screening of high-risk infants for retinopathy of prematurity (ROP) is crucial. Early screening enables prompt detection and intervention, significantly reducing the risk of visual impairment and blindness in affected babies.

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Conflicts of Interest

There are no conflicts of interest.

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