REVIEW

Current screening and diagnostic approaches of retinoblastoma in limited setting

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As the most common intraocular malignancy in children, retinoblastoma poses a vision, globe, and life-threatening risk and hence requires thorough evaluation and surveillance. While the disease is one of the most curable malignancies in established countries, children of lower-middle-income countries are not so fortunate, especially those with familial history of retinoblastoma. The delay of diagnosis proposes a grave prognosis, thus screening is a must. This study aimed to review the literature on various screening programs and applications described for the early detection of retinoblastoma, especially in a setting where genetic examination performance is limited. A literature search across PubMed®, ProQuest, and EbscoHost (MEDLINE Full text) with the topic of current methods and programs of retinoblastoma screening in neonates, infants, and children were carried out denoting various guideline and recommendations but the implementation is not uniform. Examination under anesthesia and red-reflex tests are among the most frequently conducted but the practices vastly vary especially in a place with low resources. Recent updates in mobile phone freeware should be rigorously upgraded due to its current inadequate sensitivity and specificity in detecting retinoblastoma but pose a promising future for retinoblastoma screening and diagnosis, especially in lower-middle-income countries.

Keywords: diagnostic, pediatric, retinoblastoma, screening

Introduction

Retinoblastoma (Rb) is the second most prevalent childhood cancer with an incidence of approximately 1:17,000 live births across the world [1]. The nature of ocular neoplasm in children could be different, in that it possibly invades the posterior pole and moves towards the periphery with advancing age [2]. In addition to that, advanced age could potentially be associated with optic nerve invasion, massive choroidal invasion, and anterior segment invasion which are postulated to be a higher risk of systemic metastasis and death [3,4]. While the age of diagnosis does not always guarantee that Rb is at its early stage [4], the earlier the diagnosis and therapy, the less radical forms of therapy will be performed [5]. This allows both vision and globe salvage- but most importantly life salvage [4,5]. As the survival rates increased to up to 95% of all cases in developed countries, children in low- and middle-income countries (LMIC) are often presented late and thus succumb to poorer prognosis [1,6]. A scoping review by Jain et al [7] presented contributing factors of outcome disparity in underdeveloped countries which includes lack of proper education and awareness towards Rb, inadequate infrastructures including primary health care worker capability, accessibility to proper treatment and financial support, lack of compliance, and especially national screening program. Understanding the gap can initiate the implementation of effective screening strategies [1,5,8].

Because of the disease's nature, Rb has the potential to be unidentifiable before its advanced stage [9,10]. A recent observational study showed the tendency of Rb to spread beyond the orbital area in nearly half of the subjects (256 out of 521 children) included and is diagnosed at an older age [median age 30.5 months] in children born in a low-middle income country compared to only 1.5% cancer expansion and median age 14.1 months at diagnoses in a high-income country [1] which strongly correlated with poorer prognosis hence the need for universal screening of neonates and infants especially those at risk. Herein, we review various literature regarding the impact on the detection and management outcome for patients with RB in a setting where genetic examination is scarce. We also provide a narrative review of different eye examination guidelines for suspected children with Rb in several countries.

Methods

This study aimed to review the literature across screening programs and applications described for the early detection of retinoblastoma, especially in a setting where genetic examination performance is limited. A PubMed®, ProQuest, and EbscoHost (MEDLINE Full text) search was performed to identify articles published with specific keywords such as "Retinoblastoma" and "screening" or "early detection" and "pediatric" or "children" or "child" referred to a screening for retinoblastoma yielding articles which concludes:

- Studies reporting vision screening of all newborns or pediatrics irrespective of the presence or absence of retinoblastoma risk factors
- Studies reporting RB's diagnostic methods and approaches including but not limited to mobile phone application

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Results and Discussions

Children at risk of Rb

Two out of 5 cases of Rb are hereditary, and only 10% of hereditary cases are familial [11] hence parents' unawareness of the children's eye malignancy [12] causes a delay of Rb diagnosis in the firstborn [proband] but a fortunate prognosis was pronounced in the younger sibling (non-probands) as the parents became more aware of any abnormalities of Rb [2,5] though unfortunately, the possibility of germline cases due to a new mutation with no familial history is also quite high [13]. Castela et al [14] have reviewed the complete clinical spectrum of retinoblastoma. Although genetic testing accurately defines a child's risk to develop Rb, most low- middle-income countries have no adequate resources hence the need for screening programs initiation for children at higher risk of Rb than the average population's risk for developing Rb based on conventional strategy-risk calculation considering the children's bloodline link to the proband and Rb types [unilateral or bilateral] [15].

Children with >7.5% probability pose a high risk, moderate risk ranges 1.5–7.5%, and low risk for <1%. Previous case series screened children at moderate or high risk for Rb [15], assuming the general population risk is 0.007% (one in 15,000). If there are no lesions of concern are noted, a monthly examination is preferred for children aged up to 3 months with low and intermediate risk while high-risk children aged up to 8 weeks are suggested to be examined every 2-4 weeks, monthly until age 12 months, every 2 months until age 2 years, every 3 months until age 3 years, every 4 months until age 4 years, every 6 months until age 5 years above both intermediate and high-risk children. Children with intermediate risk aged 3 to 12 months are suggested to be examined every 2 months, aged 12 to 36 months every 3 months, and aged 36 until 60 months every 4-6 months. Examination with or without sedation is decided individually based on the institution's policy and clinician preference.

Screening protocol and schedules

There are various schedules and instruments for vision acuity, ocular health, and other risk factors (such as amblyopia) screening worldwide. However, a previous systematic review denoted the difference between high-income and low-middle-income countries [16]. Higher-income countries such as Australia, Canada, and the United Kingdom start screening as early for infancy, and preschoolers; while up to 60% of middle-income countries tend to conduct screening at school age due to cost-limited resources [16]. Furthermore, higher-income countries also screen for ocular health and possible congenital disorder by specialists compared to sole vision acuity screening in middle-income countries which can be done by more general professionals or trained staff [17]. The frequency of examinations was based on the calculated risk according to previous guideline

[10] as long as no eye lesion was noted. Examination under anesthesia (EUA) provides a thorough retinal examination for any child with high and intermediate risk of Rb who was unable to participate in an office examination considering the operating ophthalmologist, pediatrician, and the child's parents decision. EUA also requires not only general anesthetic but also operating rooms, anesthesiologists, and trained nurses which could be easily obtained in tertiary centers in an established country and not LMIC. Therefore, the full dilated-eye examination is not always available, especially in LMIC [18].

Retinoblastoma Screening Guideline in Various Countries

Guide for Effective Programs in Cancer Control of the World Health Organization (WHO) stated recommendation to target populations such as children with known risk of relatives with Rb, children with leukocoria, and strabismus to be referred for 'early diagnosis' but not for 'screening' [19]. Published guidelines and policies recommend ocular examination of neonates, infants, and children [20] emphasizing the importance of red reflex examination by trained personnel [21–24]. The National Retinoblastoma Strategy (NRbS) in Canada proposes the need for regular infant vision screening through the Canadian Paediatric Society (CPS)'s guideline through regular eye screening from birth to 5 years of age[18]. To date, CPS is the only organization that explicitly proposes vision screening guidelines for Rb. Inspection of the external feature of the eyes and red reflex for newborns until 3 months of age. Infants with high risk (premature neonates, infants with hereditary ocular disease) should be referred to an ophthalmologist. An ocular alignment examination should be done in addition to previous examination policies from the age of 6 until 12 months. For children between the ages of 3 and 5 years, visual acuity testing should be conducted additionally [18].

Kenya National Retinoblastoma Strategy Best Practice Guidelines provide several referrals, diagnosis recommendations [25], and conduct screening according to CPS. The AHOPCA (Asociación Hemato- Oncológica Pediátrica de Centro America) and GALOP (Grupo de America Latina de Oncologia Pediatrica) in Latin and South America conduct guidelines as defined as the treatment, but no screening protocol or guideline. In India, identification of at-risk newborns (family history of retinoblastoma) is done through ophthalmic examination including red reflex testing using an ophthalmoscope, any abnormal red reflexes are referred to ophthalmologists which are regularly organized by Rashtriya Bal Swasthya Karyakram [26]. In Malaysia there is no screening guideline; however, every child is examined EUA with indirect ophthalmoscopy, RetCam, and ultrasonography in tertiary hospitals once they show any signs of Rb development [27]. Currently, in Malaysia, a complete eye examination is not a mandatory screening test for all newborns. The Paediatric Protocol for Malay-

sian Hospitals highlights said assessment for children with previously suspected visual impairment including a family history of cataracts and Rb. Leukocoria and squint after 6 months, frequent symptoms of Rb, are some of the 6 warning signs for visual impairment [28]. Indonesian Ministry of Health conducts no screening guideline; every child should undergo a CT-Scan or MRI every 6 months upon diagnosis according to each hospital's policies [29].

The Future of Retinoblastoma Diagnostic and Artificial Intelligence

As of today, the gold standard for Rb diagnoses is through EUA of indirect ophthalmoscopic with scleral indentation [19]. However, the procedure cannot be established as a screening tool due to various constraints -such as the need for pupillary dilatation, general anesthesia or sedation, technical expertise, and overall complicated procedure especially in children. The direct ophthalmoscope is routinely used in the red reflex examination, however, some reported the physicians' inexperience as well as the unavailability of a physician capable of using an ophthalmoscope other than an ophthalmologist [30,31]. Recently, various Rb screening through devices with Artificial Intelligence (AI), retinal, and media imaging has been proven to have the potential to screen many eye pathologies as well as RB [32–34]. Rb screening can be carried out by either simple red reflex assessment or wide-field digital retinal imaging [WFDRI] [31,35–37]. Being the easiest of all, the red reflex only poses 39% specificity and 85% sensitivity and still vastly varies among pupillary dilatation [37]. A pilot study introducing 'FOREVER' (focus on ROP, eye care, vision, eye cancer, and rehabilitation) programme in India screened 1021 presumably healthy infants shows an abnormality in 48 babies in which 0.9% require medical or surgical intervention [26], thus providing promises to be superior as it could also detect more peripheral lesions [33] but its notable high-price and limited portability enact other devices such as PEEK (Portable Eye Examination Kit) and iCAM [32–34] but lacking in the objectivity as the images need professional interpretation hence teleconsultation was introduced for accurate interpretation [34]. As parents are most of the time the first to notice any abnormalities of the eyes at home [38], a smartphone-based application comes in handy assuming at least 1 smartphone is owned by a family member; CRADLE [ComputeR-Assisted Detector of Leukocoria] and 'MD EyeCare' were later developed [39–41]. However, MD EyeCare also presents one notable drawback as it is only provided on iOS at comparably higher price smartphones. One cohort study displays eye examination using CRADLE in 20 children with leukocoria and 20 healthy controls, showing an earlier time of Rb diagnosis (117 days for unilateral Rb and 75 days for bilateral Rb) using CRADLE prototype compared to conventional examination management (408 for unilateral Rb and 114 days for bilateral Rb) [41]. The sensitivity, specificity, and accuracy of the application to detect patho-

logic leukocoria vary within age groups; 75% sensitivity at age <6 months but poorer specificity (25%) and accuracy (50%). However, the sensitivity is much higher (90%) at age <2 years [41]. EyeScreen analyzes thousand four hundred and fifty-seven participants in Ethiopia with 87% sensitivity and 73% specificity in detecting Rb. However, the sensitivity remains too low, especially for children with darker fundus pigment as red-reflex is seen duller [42]. In the future, screening and diagnosis of Rb as well as pupillary reflex interpretation and retinal imaging could be potentially aided with AIs [43].

Conclusion

Retinoblastoma is a curable disease in high-income countries. However, delay in diagnosis is highly prevalent in developing countries even though it correlates with poorer outcomes including low eye and vision salvage, the likelihood of treatment with acute or long-term toxicity, and higher mortality rates. Guidelines for the detection of RB in children' 'at risk' for retinoblastoma are vastly practiced with no definite standard, especially in lower-middle income countries. Modern screening methods- mobile phone freeware- are easy and feasible but a high false negative rate, low standardization, and the need for cross-validation encourage even more aggressive upgrades even in its free and effective-to-use quality.

Authors' contribution

NU (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Visualization; Writing – original draft; Writing – review & editing)

DK (Conceptualization; Investigation; Supervision; Writing – review & editing)

SM (Investigation; Supervision; Validation; Writing – review & editing)

PP (Data curation; Formal analysis; Investigation; Methodology; Writing – review & editing)

Conflict of interest

The authors declare no competing interest.

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