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Evaluation of the red reflex: An overview for the pediatrician

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Abstract

BACKGROUND

Red reflex test (RRT) is a simple, non-invasive method that can be performed easily by pediatricians during the clinical examination in neonatal period, infancy and childhood. Abnormal reflexes can lead to prompt diagnosis of several ocular disorders, with potentially severe consequences on patient's vision, cognitive function and even life.

AIM

To underline the contribution of pediatricians to early detection of vision and life threatening diseases by using RRT effectively.

METHODS

For the present systematic review, PubMed searches were performed using the key words "red reflex and newborn"; "red reflex and neonate"; "red reflex and complications"; "red reflex and necessity"; "red reflex and retinoblastoma"; "red reflex and congenital cataract"; "red reflex and glaucoma"; "red reflex and prematurity"; "red reflex and leukocoria"; "red reflex and blindness"; "red reflex sensitivity and specificity"; "red reflex and differential diagnosis"; "red reflex and guidelines". The relevant articles were selected without language restrictions. When a full-text publication was not available, their English abstracts were used. In some cases, studies from the reference lists of the selected articles provided useful information. The research took place in September 2020, in the Ophthalmology Department of University Hospital of Alexandroupolis.

RESULTS

A total of 45 articles were selected according to the used key words. After reviewing data from these articles, it is supported that red reflex remains an effective tool of undeniable importance for early detection of severe eye conditions, such as cataract, retinoblastoma, retinopathy of prematurity and glaucoma. Although literature reports some limitations of RRT, including a notable percentage of false positive tests, the inability to detect small, peripheral retinoblastomas and the lower sensitivity for posterior segment pathology, it is widely accepted that the benefits from the regular evaluation of the test on public

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health are significant. Therefore, RRT has been established by international guidelines and should be an essential component of pediatricians clinical practice. Red reflex implementation should be incorporated in pediatricians educational programs, so that they would be able to provide quality services and safe diagnoses.

CONCLUSION

The implementation of RRT should be encouraged in all neonatal/pediatric departments. Prompt education of pediatricians should be empowered in order to achieve careful vision screening, according to current guidelines.

Key Words: Red eye reflex; Leukocoria; Visual screening; Newborn; Prevention; Pediatric examination

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Core Tip: Red reflex test (RRT) is an easy, non-invasive examination that enables detection of vision- and life-threatening eye disorders. Various studies have dealt with the effectiveness, sensitivity/specificity and abnormalities of the RRT. The aim of the present review is to emphasize the advantages of RRT implementation from neonatal period to childhood and to underline the pediatricians' role in early diagnosis and treatment of the aforementioned diseases. This study presents a practical guide for the evaluation of the RRT, based on literature data. With appropriate education and compliance to the vision screening protocols, the pediatric society could reduce the incidence of preventable pediatric blindness.

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INTRODUCTION

The first few weeks of life are of paramount importance for the development of visual function, thus the assessment of newborns' visual system should be part of the routine clinical examination. Numerous eye disorders of the neonatal and childhood period can lead to permanent visual impairment, even to blindness and loss of life[1].

It is worth mentioning that about 75% of blindness cases are preventable[2], a fact that emphasizes the need for early detection of the sight threatening conditions. Congenital infections, metabolic and chromosomal disorders and inheritance are among the most common causes of childhood blindness[3]. Therefore, eye examination should begin in newborn infancy and be continued as a part of the routine pediatric examination in order to achieve early diagnosis, prompt treatment and better prognosis.

The red reflex test (RRT), which was firstly introduced by Bruckner in 1962[3], is an effective, non-invasive examination that contributes to the diagnosis of various eye diseases, such as cataract, glaucoma, retinoblastoma and retinal disorders[3,4]. The RRT is easily performed in a darkened room by holding a direct ophthalmoscope, focused on the patient's pupil, with a lens power at "0", from a distance of approximately 30-45 cm (12-18 in)[4,5]. The normal RRT should be symmetric in both eyes, round, bright reddish-yellow or light grey in darkly colored eyes. Any asymmetry or lack of a red reflex, white reflexes or dark spots are abnormal and require referral to ophthalmologists[4,6]. The main causes of red reflex abnormality include congenital cataract, opacity of the cornea, iris abnormalities, vitreous opacities, tumors or chorioretinal malformations[6].

According to the latest suggestions of the American Academy of Pediatrics (AAP) and the American Association for Pediatric Ophthalmology and Strabismus (2016) the RRT should be performed at every well-baby visit from newborn to 6 mo age, afterwards, at 12 mo, 1-3 years, 4-5 years and 6 years and older[7,8].

The primary objective of this article is to provide an updated review on RRT published literature and highlight its importance in the detection of potentially sight threatening or even life threatening ocular diseases.

MATERIALS AND METHODS

Study design and selection criteria

This systematic review met the statements checklist of the Preferred Reporting Items for Systematic Reviews (PRISMA)[9]. The selection criteria were defined by applying the Problem/Population, Intervention, Comparison and Outcome framework. Articles were screened by title and abstract, according to the following inclusion criteria: Articles focused on the contribution of the RRT in diagnosing pathologic conditions, articles on RRT sensitivity and specificity, articles on guidelines about RRT and articles focused on compliance with RRT recommendations. Articles referring to adult patients were excluded. All of the eligible articles provided valuable information about the usage of the RRT in pediatric clinical practice.

Literature research strategy

A systematic search on PubMed databases was performed by two reviewers (A.T. and A.P.) in September 2020. Search terms used in this review are presented in Table 1. The initial search was performed without search filters and language restrictions. When the eligible articles were not available in full text in English, abstracts were used as a source of information. The date of publication was not an exclusion criterion. Additionally, the reference lists of the eligible articles were checked, and articles that met the inclusion criteria and provided useful information were also selected.

Study selection and quality assessment

A total of 45 articles that were relevant to the topic of interest and exclusively referring to the pediatric population were finally selected. Afterwards, the eligible articles were scanned diligently and independently by the two reviewers and the following data were extracted: Correct evaluation of RRT, correlation between RRT and certain ocular diseases (such as retinoblastoma and congenital cataract) and compliance and limitations of RRT. Any conflict was dissolved by a third reviewer (G.L.). Risk of bias of the eligible articles was conducted with "Quality Assessment Tool for Quantitative Studies" by Effective Public Health Practices[10]. Again, the same two individual reviewers assessed the articles, blinded to each other's decisions, and a third reviewer resolved any conflict. The results are demonstrated in Table 2.

RESULTS

Literature review returned 45 articles that met our inclusion criteria. They covered the whole spectrum of the topic in interest. The final selection of the eligible papers are presented in Table 1. Detailed data on the articles are shown in Table 3.

Diagnostic procedure of RRT

The evaluation of RRT is an easy, low-cost method that can be performed by pediatricians and other first care physicians in order to provide early diagnosis of severe pathologies. A necessary precondition that allows valid diagnoses is the appropriate training of medical students and trainee pediatricians during the years of specialty. For ideal performance of the test, it is essential to keep the room completely darkened (to maximize pupil dilation) and the direct ophthalmoscope fully charged. The lens power should be set at "0", unless there is a refractive error of the clinician's eyes. In this case, she/he could examine without wearing spectacles, by holding the ophthalmoscope closely to the examiner's eye and dialing the spectacle corrective power into the instrument. A practical way is to look through the peephole and dial the lenses till a pure image is viewed. The clinician should sit at a distance of approximately 0.5 m, but it could be increased in case of a nervous or uncooperative child. The co-axial position of the examiner is appropriate for estimating the RRT, however, it may not reveal ocular pathologies of small dimensions in peripheral areas. Therefore, the pediatrician needs to perform the RRT by using different angles along the horizontal meridian of the retina in order to assess the nasal and temporal retina by oblique viewing[4,5,11]. It is quite easy to perform, even in younger patients, as after

Table 1 Search terms

RRT and neonate/newborn	RRT congenital cataract
RRT and complications	RRT retinoblastoma
RRT and necessity	RRT and glaucoma
RRT and sensitivity and specificity	RRT and blindness
RRT and differential diagnosis	RRT and leukocoria
RRT guidelines	RRT and prematurity

RRT: Red reflex test

evaluating the red reflex from a co-axial position, the pediatrician should make the patient look in different directions. It may be helpful for the examiner to make the child focus behind the examiner's back by using a light or a toy. In case of infants or newborns, parents should hold the baby with a "chair hold" manner. This may keep the baby calm and able to focus the gaze straight forward. In this way, the examiner could perform the RRT without opening the baby's eyes with her/his hands. Taking into account that in the first days of life it is hard for the neonates to fixate or even to open their eyes, pediatricians should have plenty of patience and time in order to evaluate RRT safely.

A normal RRT consists of symmetrical bright red reflexes of both eyes, indicating that the ocular media (cornea, aqueous humor, lens, vitreous body) are transparent. A reduced or absent red reflex indicates an obstacle to the anatomical path to and from the retina (Table 4)[12].

Despite its name, the "red" reflex is often normally yellow, orange, red or any combination of these colors. In some patients with darker complexion, an increased pigmentation of the eye could be the cause for less bright reflex. Therefore, many variations among different racial or ethnic groups may be observed. Thus, examination of the parents would set the normal baseline[4,12].

In any case of atypical coloration of the red reflex, pediatricians should take into account many parameters and risk factors, such as gestational age, birth weight, use of oxygen therapy, phototherapy, blood transfusion and conjunctivitis, that could significantly affect the development of vision problems and subsequently the result of RRT[2]. Black reflex, which is suggestive of corneal scar, cataract or intraocular hemorrhage, and asymmetrical or non-homogenous reflexes require further investigation[13]. Asymmetry in the refractive power of the eye may cause asymmetrical red reflexes and should be checked, because any delay could lead to amblyopia and loss of vision[7]. Refractive errors may also give a yellow-white edge to a red reflex[14].

A white pupillary reflex is characterized as leukocoria, from the Greek words "leucos" (white) and "kôre" (pupil). White pupils are often noted by parents and described as something white, shiny, jello-like or a discoloration of the eye. This finding is pathological. Therefore, its presence is always concerning and requires urgent referral to an ophthalmologist. The most common cause of leukocoria in newborns is congenital cataract[15], while the most ominous pathology is retinoblastoma[16]. Other causes of leukocoria are presented in Table 3[15].

Pharmaceutical pupil dilation before performing RRT remains a controversial issue. Some infants and young children may have small pupils and restricted fixation, making the ophthalmoscopy a difficult examination. Moreover, patients with risk factors, such as family history of retinoblastoma or cataract, need a thorough evaluation of RRT in order to exclude any possibility of pathological lesions. In these cases, dilation of pupils could enhance the evaluation of RRT. In a survey by Ozkurt *et al*[17], RRT without pupillary dilation presented a positive predictive value of 70%; as without dilation, 2.2% of newborns presented an abnormal RRT. After dilation, ocular pathology that caused an abnormal RRT was detected in 1.5% of these neonates. For many years, pupil dilation has been used by pediatric ophthalmologists on infants over 2 wk on a routine basis. However, the pharmaceutical agents used for dilation (phenylephrine, anticholinergic agents such as cyclopentolate hydrochloride, tropicamide) were occasionally associated with significant complications. The reported adverse effects include elevated blood pressure and heart rate, urticaria, cardiac arrhythmias, and contact dermatitis. It is worth noting that extra caution is needed in cases of preterm infants, as they presented increased sensitivity to the aforementioned dilating eye drops[4]. Thus, the last policy statement of the AAP in 2016 clarified that if

Table 2 Quality assessment

Ref.	Year	Selection bias	Study design	Confounders	Blinding	Data collection methods	Withdrawals and drop-outs	Global rating
Nye[1]	2014	Moderate	Weak	Strong	Moderate	Weak	NA	Weak
De Aguiar <i>et al</i> [2]	2011	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Eventov-Friedman <i>et al</i> [3]	2010	Moderate	Weak	Strong	Moderate	Strong	NA	Moderate
AAP[4]	2008	Moderate	Weak	Strong	Moderate	Weak	NA	Weak
Litmanovitz <i>et al</i> [5]	2010	Moderate	Weak	Strong	Moderate	Weak	NA	Weak
Cagini <i>et al</i> [6]	2017	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Loh <i>et al</i> [7]	2018	Moderate	Weak	Weak	Moderate	Weak	NA	Weak
Donahue <i>et al</i> [8]	2016	Moderate	Weak	Weak	Moderate	Weak	NA	Weak
Li <i>et al</i> [11]	2010	Weak	Weak	Weak	Moderate	Weak	NA	Weak
Gurney <i>et al</i> [12]	2018	Weak	Weak	Weak	Moderate	Weak	NA	Weak
Levin[13]	2015	Weak	Weak	Weak	Moderate	Weak	NA	Weak
Sloot <i>et al</i> [14]	2015	Moderate	Weak	Weak	Moderate	Weak	NA	Weak
Wan <i>et al</i> [15]	2014	Weak	Weak	Weak	Moderate	Weak	NA	Weak
Tuli <i>et al</i> [16]	2011	Moderate	Weak	Weak	Moderate	Moderate	NA	Weak
Ozkurt <i>et al</i> [17]	2018	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Bell <i>et al</i> [19]	2014	Moderate	Weak	Weak	Moderate	Weak	NA	Weak
Balmer <i>et al</i> [20]	2007	Moderate	Weak	Weak	Moderate	Weak	NA	Weak
Mansoor <i>et al</i> [21]	2016	Moderate	Weak	Weak	Moderate	Weak	NA	Weak
Popoola <i>et al</i> [22]	2019	Moderate	Weak	Weak	Moderate	Weak	NA	Weak
Abramson <i>et al</i> [23]	2003	Moderate	Weak	Weak	Moderate	Strong	NA	Weak
AAP <i>et al</i> [24]	2002	Moderate	Weak	Weak	Moderate	Weak	NA	Weak
Li <i>et al</i> [25]	2013	Strong	Weak	Strong	Weak	Strong	NA	Weak
Butros <i>et al</i> [26]	2002	Moderate	Weak	Weak	Weak	Weak	NA	Weak
Sun <i>et al</i> [28]	2016	Strong	Weak	Strong	Weak	strong	NA	Weak
DerKinderen <i>et al</i> [29]	1989	Moderate	Weak	Strong	Weak	Strong	NA	Weak
Goddard <i>et al</i> [30]	1999	Moderate	Weak	Strong	Weak	Strong	NA	Weak
Bhatti <i>et al</i> [31]	2003	Moderate	Weak	Weak	Moderate	Moderate	NA	Weak
Rajavi <i>et al</i> [32]	2016	Moderate	Weak	Weak	Moderate	Weak	NA	Weak
Gogate <i>et al</i> [33]	2011	Weak	Weak	Weak	Moderate	Weak	NA	Weak
Haargaard <i>et al</i> [34]	2015	Moderate	Weak	Strong	Moderate	Weak	NA	Weak
Atiq <i>et al</i> [35]	2004	Weak	Weak	Strong	Moderate	Weak	NA	Weak
Meier <i>et al</i> [36]	2006	Moderate	Weak	Strong	Moderate	Weak	NA	Weak
Donahue <i>et al</i> [37]	2016	Moderate	Weak	Weak	Moderate	Strong	NA	Weak
Mndeme <i>et al</i> [38]	2010	Moderate	Weak	Strong	Moderate	Strong	NA	Moderate
Magnusson <i>et al</i> [39]	2013	Moderate	Weak	Strong	Moderate	Strong	NA	Moderate
Özkurt <i>et al</i> [40]	2019	Moderate	Weak	Weak	Moderate	Strong	NA	Weak
Ulanovsky <i>et al</i> [41]	2015	Strong	Weak	Strong	Moderate	Moderate	NA	Moderate
Raoof <i>et al</i> [42]	2016	Weak	Weak	Weak	Moderate	Strong	NA	Weak
Wall <i>et al</i> [44]	2002	Weak	Weak	Weak	Moderate	Strong	NA	Weak

Gupta <i>et al</i> [45]	2019	Weak	Weak	Strong	Moderate	Weak	NA	Weak
Munson <i>et al</i> [46]	2019	Moderate	Weak	Weak	Moderate	Moderate	NA	Weak
Chen <i>et al</i> [52]	2019	Moderate	Weak	Weak	Moderate	Strong	NA	Weak
AAP[53]	2003	Moderate	Weak	Strong	Moderate	Weak	NA	Weak
Anderson[54]	2019	Moderate	Weak	Weak	Moderate	Weak	NA	Weak

NA: Not applicable.

Table 3 Data extracted from the eligible articles

	Total number of articles	Ref.
Emphasis on the importance of RRT	44	[1-8,11-17,19-26,28-42,44,46,52-54]
Retinoblastoma	20	[3,6,11,12,15-17,19-23,26,28-30,36,38,40,54]
Congenital cataract	16	[3,5,6,12,15-17,19,21,31-35,38-40]
Retinopathy of prematurity	4	[2,3,16,20]
Specificity and/or Sensitivity of RRT	10	[3,5,6,11,12,22,25,28,32,38]
Compliance of health care providers with current screening protocols	12	[2,3,5,6,14,22,23,32,39,40,42,44]
Limitations of RRT	9	[1,4,6,11,12,23,26,28,41]
Comparison of RRT with other techniques	7	[17,25,28,34,38,45,46]

RRT: Red reflex test.

Table 4 Anatomical approach for an abnormal red reflex test[4,12]

Tear film	Mucus or other foreign bodies
Cornea	Dysgenesis of the anterior segment (Peters anomaly), congenital glaucoma, birth trauma
Lens	Cataract
Vitreous	Persistent fetal vasculature, vitreous hemorrhage or inflammation
Retina	Retinoblastoma, retinal detachment, Coat's disease, chorioretinalcoloboma, toxocariasis
Other	Anisometropia, strabismus

the pediatrician provides conditions of a fully darkened room, further pharmaceutical dilation is not necessary. Abnormal findings in RRT including dark spots, absent or significantly reduced reflex, leukocoria, or any asymmetry of the reflexes are indications for referral to an ophthalmologist with experience in children for thorough dilated fundus examination[8].

Retinoblastoma

Retinoblastoma is a neuroblastic tumor of the retina, with an incidence of approximately 1:20000 live births per year, which can lead to blindness, metastatic disease and loss of life[18,19]. The onset of the disease may occur *in utero* and up to 4 years of age[20]. It was estimated to be responsible for 17% of all neonatal cancers[15,20]. Sixty percent of retinoblastomas are non-heritable, usually unilateral[21,22]. Studies recorded positive family history in only 15%-25% of patients[19,22]. Typically, heritable retinoblastomas are bilateral, usually presented within the first year of life, with better visual potential in the eye with the smaller tumor size. According to literature data, the most common reason that concerned the family was the presence of leukocoria (initial sign in 50%-60%), often observed on flash photographs. Other manifestations included strabismus (initial sign in 20%-25%), inflammatory signs (initial sign in 6%-10%), *e.g.*, painful/red eye, tearing, heterochromia and hyphema[15,18,20,23]. In 50% of the cases worldwide there were extraocular signs and symptoms, which were associated with poorer survival rate (0%-50% *vs* 95%)[23].

Currently, the RRT is the main screening tool used by primary care physicians for the detection of retinoblastoma[24]. Li *et al*[25] reported a case of a 3 d old newborn with retinoblastoma, as the youngest patient with the disease. Notably, the median age of retinoblastoma diagnosis is 24 mo[8,26]. Therefore, the RRT should be performed by the pediatrician on a regular basis at every age, from birth to childhood. During the clinical examination, leukocoria seen on RRT is the primary sign that sets the suspicion for retinoblastoma[20]. A normal RRT is not equal with the absence of retinoblastoma[27]. According to some studies[26,28], peripheral or small tumors could give falsely normal RRT, while larger tumors were generally detected by RRT. The studies underlined that early diagnosis *via* RRT implementation and prompt treatment of retinoblastoma were associated with better prognosis and higher cure rate (95%)[18,19].

Delayed detection increases the possibility for larger tumors and metastases, rendering the treatment significantly more aggressive and costly, with no certain outcome[20]. More specifically, an 8-wk-delay after the onset of signs and symptoms led to elevated risk of local invasion[29] and a 6-mo-delay highly increased the extraocular extension risk[30]. Untreated retinoblastomas are fatal[18,19]. A recent study reported that in most cases (80%), the parents firstly noticed the presenting signs of retinoblastoma and not pediatricians (8%) or ophthalmologists (10%)[23]. Possible explanations for these findings included (1) The difficulty to evaluate peripheral tumors with RRT performed by co-axial position *vs* more opportunities for the family members to view the eye from multiple angles; (2) Underutilization of well-child care visits; (3) A not dark enough pediatric office during RRT; (4) Uncooperative child; (5) Miotic pupils; (6) Inappropriate RRT technique, lack of education; and (7) Low clinical suspicion[23]. Another study mentioned delayed referral from the primary care physicians to specialists in 1/3 of the cases, due to justification of the presenting signs as normal findings or as part of other diagnosis. An additional reason for delayed therapy was the time spent by parents seeking treatment. The family unwittingly contributed to the delay in 77% of patients[26].

It is also emphasized that the pediatricians must have the education and skills to identify and refer to specialists a patient with the suspicion of retinoblastoma, in prompt time[26]. It has to be clear to all pediatricians that a positive family history of retinoblastoma, regardless of the RRT result, is an absolute indication for ophthalmologic examination in newborn nursery. Afterwards, regular ophthalmologist evaluations must be arranged, with aggressive surveillance and communication between the supervisor pediatrician and ophthalmologist until at least 28 mo of life. In case of revealed tumor, the follow-up should be continued until at least the age of 7 years. Additionally, the observation of eye abnormalities (leukocoria, strabismus) by the family, at any age, regardless of the RRT results, requires similar investigation to rule out any possibility for malignancy[23,26].

Congenital cataract

Congenital cataract is the opacification of the crystalline lens, which can be present at birth or develop within the first 3 mo of life. According to published literature[6,21,31-33], the incidence of congenital cataract ranges between 0.6 to 15 per 10000 live births, while it was estimated to be responsible for approximately 10% of childhood blindness [3]. In most cases, the etiology remains unknown. Inheritance is involved in 25% of congenital cataracts (autosomal dominant pattern). Other causes include chromosomal abnormalities (trisomy 21, trisomy 18), metabolic disorders (*e.g.*, galactosaemia) and congenital infection syndrome (toxoplasmosis, cytomegalovirus, syphilis, rubella, herpes simplex virus, varicella zoster virus)[21]. It is worth mentioning that most unilateral cataracts are isolated anomalies, however, 20% of cataracts attributed to congenital rubella are unilateral. Bilateral cataracts that are not correlated with genetic mutations need further investigation to exclude systemic disorders[15].

Early detection and treatment of congenital cataract have become a priority of the Global Vision 2020 initiatives of the World Health Organization[6]. The RRT is a highly sensitive screening test for congenital cataract. Cagini *et al*[6] performed RRT screening on neonates up to 3 d old, over a period of 3 years, indicating a congenital cataract rate of 0.009%. Haargaard *et al*[34] indicated the superior sensitivity of RRT compared to other diagnostic techniques in the detection of congenital cataract. The absence of red reflex during the routine neonatal eye screening could reveal early diagnosis of congenital cataract. This finding requires a thorough systemic clinical examination and the appropriate investigation to rule out every common or rare condition causing congenital cataract. Atiq *et al*[35] presented a case report of a 5-mo infant with bilateral congenital cataract, which at birth was investigated only for rubella and galactosemia. In the months that followed, the progressive clinical status

(including delayed motor milestones, irritability, sweating during feeding, generalized hypotonia, supraventricular tachycardia) and the family history of neonatal deaths, in combination with detected lactic acidosis and hypertrophic cardiomyopathy led to the diagnosis of Senger's disease. Other clinical findings that would empower the suspicion for cataract include nystagmus, absence of interest for surroundings and inability to fix and follow[21].

The time of detection of congenital cataract is crucial for the visual outcome following surgery, since early therapeutic intervention before the age of 6 wk for unilateral cases and 8 wk for bilateral cataracts was associated with best visual outcome[6,32]. Any delay on the detection and treatment of congenital cataract could give rise to severe consequences in visual evolution, even blindness or amblyopia, which has considerable impact on the neurobiological development of the children. In Bhatti *et al*[31] study, more than half of the infants with isolated cataract were diagnosed during the first 6 wk of life, but 38% of them were detected later, with a percentage of 15% after the age of 5 mo. The findings above underlined the importance of the method in detecting the cases of congenital cataract.

Retinopathy of prematurity

Retinopathy of prematurity (ROP) is a vasoproliferative disorder that affects premature babies, especially those with low weight of birth[2]. In Meier *et al*[36] study, ROP was responsible for 12% of leukocoria cases. Gestational age of less than 30 wk, birth weight less than 1500 g, history of oxygen therapy, septicemia and blood transfusion are among the most prevalent risk factors for the development of this potentially vision threatening disease[2,16]. The first clinical finding that could be observed in these newborns is the demarcation line, (Stage 1) which indicates the difference between avascular and vascularized retina. As the disease progresses, capillary growth begins at the edges of the demarcation line leading to the formation of "ridge" (Stage 2); the development of fibrovascular proliferation from the ridge into the vitreous body constitutes the third stage of ROP. From this stage, fibrovascular membrane may be grown posteriorly causing tractions and thus partial (Stage 4) or total retinal detachment (Stage 5)[20]. It becomes clear that advanced stages are equal with severe and permanent visual impairment. Therefore, careful examination of all preterm infants from pediatric ophthalmologists is of great clinical importance and has to be emphasized and encouraged from pediatricians[37]. It is worth noting that leukocoria may be detected after Stage 3 of ROP, however, the RRT performed by pediatricians or primary care physicians and the early referral of all suspicious cases may save the vision of a neonate as early implementation of laser or cryotherapy on peripheral retina protects the central retina from damage[16].

Sensitivity and specificity of RRT

Several studies have dealt with the sensitivity and specificity of the RRT. The estimated rates of sensitivity and specificity of RRT without pupillary dilation immediately after birth were 85% and 38.5% respectively for the diagnosis of any congenital ocular disorder[32]. Concerning the early diagnosis of congenital cataract and retinoblastoma, the RRT was proved to be a useful tool, with high rates of estimated respective sensitivity (100%) and specificity (97.9%). However, researchers identified a remarkable percentage of false positive tests (2%) and a positive predictive value of 0.7%[6]. On the contrary to these findings, another study revealed a much smaller percentage of false positives (0.0006%), with a positive predictive value of 42%[3]. Furthermore, Sun *et al*[28] evaluated the sensitivity and specificity of RRT in the detection of anterior (cornea, iris, aqueous humor or lens) and posterior (vitreous body, retina, choroid, optic nerve) ocular disorders. They considered the RRT as a useful diagnostic tool for diseases located on the anterior segment of the eye, since it detected 99.6% of the anterior pole anomalies (*vs* 4.1% of the posterior pole diseases). Therefore, RRT presented high rates of overall specificity (95%), but low overall sensitivity (13.9%). The rates of RRT sensitivity and specificity may range depending on the circumstances. Rajavi *et al*[32] found a significant increase of false positive RRT when newborns were examined by pediatricians in the first hours of life, under non-standard conditions (at the delivery room, beside mother and without pupil dilation), in comparison with the examination that took place by ophthalmologists, on the third day of life, under standard conditions (dark room and dilated eyes). In this study, the RRT sensitivity was 85% and specificity 38.5%, when performed under non-standard conditions. The results could be explained by the lack of experience of the pediatricians and by the ocular and tear film problems that usually disappear within a few days after birth. However, the researchers underlined that better conditions could make the evaluation of RRT more accurate.

Importance of the RRT

All of the eligible articles of the present review unanimously pointed out the value of the red reflex examination as an efficient tool for early diagnosis of pediatric ocular diseases, achieving prompt treatment with better outcomes. At this point, the literature highlights the unique role of pediatricians, who own the advantage not only to contribute to the improvement of the course of eye diseases and of the quality of patients' lives but also to save lives of children with severe diseases, such as retinoblastoma. The low incidence of retinoblastoma might reassure the general pediatrician. Nevertheless, the fact that plenty national newborn screening programs include tests for rare diseases, such as phenylketonuria (1/18000) and galactosemia (1/57000), indicates that early detection of severe diseases could prevent grave consequences for the economies, the health care systems and also for the quality and even the existence of the patient's life[26]. Similarly, applying RRT correctly could prevent the bad outcomes of delayed detection of retinoblastoma.

The performance of the RRT, from infancy and at every well child visit, following current pediatric guidelines could prevent childhood blindness[3,38]. Literature data correlated the RRT with early detection of congenital cataract. In Sweden[39] RRT seemed to be performed at the maternity ward at high rates (90%), a fact that was connected with an increase in the percentage of early detection and treatment of patients with congenital cataract. More specifically, 75% of the children who underwent surgery before the age of 1 year were cases with diagnosis and treatment before the sixth week of life. Another study[34] dealt with the 5-year experience of the different eye screening protocols of Sweden and Denmark. The results revealed a significantly higher rate of prompt diagnosis of pediatric cataract, when RRT was performed at maternity wards, in comparison with the absence of RRT. A survey in Tanzania concluded the same results[38]. The need for implementation of red reflex screening is even stronger in Turkey, the Middle East, Asia and Africa. Countries with high rates of consanguineous marriages showed significant correlation with red reflex abnormality (Turkey: 70.6% of neonates with abnormal RRT with a history of parental intermarriages *vs* 29.4% among normal reflexes), which was related with higher prevalence of genetic causes of common pediatric ocular diseases[17]. In a Turkish study[40], 72% of the pediatricians questioned considered that they should add RRT to follow-up charts, as they do for somatometric data. After all, pediatricians should be aware and well educated on including RRT in their routine clinical practice, as the importance of this method is to enable them to assess the quality of the transparent media of the eye, in an easy, non-invasive, low-cost manner[2].

Limitations of RRT

Although RRT remains a useful method for detecting severe pediatric ocular diseases, it has to be noticed that it also has some drawbacks. It has been emphasized that abnormalities of RRT have to be referred to ophthalmologists. However, a normal RRT does not exclude ocular pathology. First of all, the RRT enables the evaluation of only a small area and not the whole retina[11]. Thus, abnormal lesions, including retinoblastoma, could be missed when they are of small size or situated peripherally[12,26,28]. It is worth mentioning, that the detection of such cases was significantly improved while using additionally oblique viewing of the fundus and even more with pupil dilation[11]. Nevertheless, some tumors could still be missed. So, patients at high risk of retinoblastoma or other eye disorders leading to leukocoria (*e.g.*, family history of retinoblastoma, infantile or juvenile cataracts, retinal dysplasia, glaucoma) should be evaluated by specialists, regardless of the RRT result[4,11]. Moreover, RRT cannot diagnose some disorders of the retina or the optic nerve, which cause visual impairment, such as retinal dystrophy or optic atrophy. As a result, cases with impaired vision demand ophthalmologist's investigation, despite a normal RRT[12]. In another survey[28], RRT was unable to detect some fundus abnormalities, such as pigment, vascular, hemorrhage and subretinal exudative changes. Furthermore, the researchers proved that the accuracy of RRT in diagnosing disorders of the posterior pole of the eye was significantly lower than those of the anterior pole[12,28]. Literature data also recorded a limitation of the RRT in the neonatal period, enforcing the recommendations for repetition of the test routinely. Sun *et al*[28] reported some newborns with normal RRT in the first days of life who were diagnosed with familial exudative vitreoretinopathy after abnormal RRT or presence of nystagmus at the age of 1-6 mo. Performing RRT on a newborn or an infant's eyes could be a difficult challenge for inexperienced pediatricians. An infant's pupils are small and difficult to assess, so that physicians' complaints usually include "infant is uncooperative", "eyelids are closed tightly" or "unable to evaluate red reflex"[1]. However, these

statements are unacceptable and dangerous and underline the need for education to provide the RRT procedure effectively in order to avoid undesirable consequences. Ulanovsky *et al*[41] performed a retrospective observational study including 18872 neonates born from 2008 to 2011. During the years that RRT was performed, the researchers found a significantly higher incidence of clinical conjunctivitis with positive bacterial culture. This result was correlated with direct contact of the examiner's hands with newborns' eyes, hence the avoidance of direct contact with neonates during the RRT should be the general rule.

Despite the reported high levels of sensitivity for certain ocular diseases, false positive results (reduced red reflexes on eyes without abnormalities) were not unusual in the literature. Cagini *et al*[6] noticed high rates of false positives (only 3 of 461 patients with a positive or equivocal test were diagnosed with a congenital disease). On the contrary, another study recorded a much lower percentage of false positives (1 of 1643 tests was false positive)[6]. Inexperienced examiners, inappropriate equipment, small pupils, strongly pigmented fundus and conditions during the diagnostic procedure could explain the high rates of false positives[12,32]. However, the researchers considered the RRT essential part of the neonatal eye screening, as it provided early detections with high sensitivity rates[6].

Compliance with RRT guidelines

Although the necessity and effectiveness of RRT have been supported by international guidelines, data from the literature revealed insufficient implementation of the examination. Raoof *et al*[42] assessed the performance of RRT from health care professionals (general practitioners, midwives, pediatricians) *via* questionnaire. They found that 10% of responders admitted implementation of the test only when they had the time or when the parents were worried. Despite the fact that New Zealand's guidelines clearly define the appropriate time of red reflex examination, the majority of professionals (50.1%) seemed to perform the RRT at 6 wk age. Only 17.3% of the responders had received formal training for RRT, while 16.6% declared to feel underconfident during the examination[42]. Moreover, 46.1% of the neonatal units in Israel performed RRT during the years 2007-2008, while in Sao Paulo Brazil, the relative percentage was 81% during 2004[3]. Another study measured the lowest number of RRT evaluations at the high-risk neonatal units, and this finding was attributed to the unstable health status of the neonates[43]. Wall and colleagues[44] investigated the compliance of the pediatricians with vision screening guidelines. They found that a significant part of the pediatricians did not examine red reflexes beyond 6 and 24 mo of age (23% and 44%, respectively). The reasons for non-compliance seemed to be multifactorial and included the lack of time, patience, education, skills and also some worries about adequate reimbursement for vision screening[44]. Additionally, the limited staff and the perception of the pediatricians that the RRT was not their responsibility were also among the reported causes[3]. Moreover, several environmental factors could affect physician and patient compliance on RRT implementation. Nowadays, cataract remains one of the most usual reasons of preventable blindness in middle-low income countries, with very poor post-surgery visual outcomes. In these countries, late presentation of patients was very common[38]. A survey in East Turkey mentioned that 19% of pediatricians did not have an ophthalmoscope or did not know how to use it[40].

RRT and other techniques

Nowadays, RRT is a part of visual screening, supported by official guidelines for the pediatric community. However, the last recommendations published by the World Health Organization (WHO) did not include RRT but the pencil light examination. Literature provided controversial data regarding this method. Concerning the torchlight, Mndeme *et al*[38] strongly recommended that WHO guidelines should replace torchlight examination with RRT using direct ophthalmoscope due to the very low sensitivity rates (7.5%) of torchlight. Moreover, a Turkish study[17] emphasized that pencil light illumination should not be used by pediatricians and general practitioners, as this method missed most of the cases with congenital cataract. On the other hand, the researchers made it clear that RRT should become an essential part of the national pediatric eye screening protocol. Haargaard *et al*[34] studied the different protocols for congenital cataract screening that were used in Sweden and Denmark during 2008-2012. In 2011, Denmark introduced the pencil light as the screening tool for detection of congenital cataract at 5 wk of life, without any change in the age of diagnosis to be noted, in comparison with the absence of screening previously. On the other hand, the disease was detected significantly earlier in Sweden, where the RRT was a part of routine newborn examination.

Mndeme *et al*[38] dealt with three alternatives to the standard direct ophthalmoscopy for the evaluation of red reflex and also compared the standard RRT with the torchlight examination. The first tool was ArchLight, an easy and cheap device that uses a light emitting diode (LED). The second device was Peek Retina, an adaptor for smartphones, with prisms and LED that allows examination of the retina snaps and differentiation of normal and abnormal red reflexes *via* the coaxial light source. Thirdly, CatCam device, a prototype comprising a modified smartphone with a coaxial infra-red LED and infrared sensitive camera, provides evaluation of fundus reflex without causing miosis. All three methods had very high sensitivity (over 90%) and specificity (86.7%-100%), with the CatCam performing the best, followed by the Archlight and then the Peek Retina. The CatCam could improve the accuracy of pediatric cataract diagnosis; however, it still remains expensive and commercially unavailable. On the other hand, the Archlight is easily performed on infants, with much lower cost. These new technologies could strengthen the accuracy of RRT and make it easier and more feasible to the medical community.

Digital images analysis could provide an opportunity for telemedicine as well. However, it was underlined that more investigation of their efficacy on detecting pediatric ocular disorders is required. Another study[25] included advanced digital fundus imaging using RetCam during the eye screening of newborns. The digital examination revealed a significant number of well-being neonates with abnormal ocular findings, which RRT was unable to detect. The most common among them was retinal hemorrhages, a usually benign and transient condition after birth trauma. However, more studies need to be performed to investigate any correlation between early fundus findings and final visual impairment. Smartphone photography for the detection of amblyogenic conditions in children 5-8 years of age, through snaps of pupillary red reflexes, was the objective of Gupta *et al*[45] trial. All high refractive errors were detected with success, however, moderate errors revealed false negative results. The sensitivity of the photographs for all other ocular diseases was 100%. The usage of smartphones should be further investigated in all ages and for more eye disorders in order to provide a low-cost, effective screening tool for developing countries. It has been reported[23]for more than 90% of leukocoria cases that the family firstly noticed the presence of white pupils in photographs. Munson *et al*[46] dealt with a tool based on red reflex of the pupils that could provide to parents the detection of leukocoria earlier. They presented a novel application for smartphones, the CRADLE, which can be downloaded for free and allows early detection of leukocoria. More specifically, the application creates a private storage of photographs and after digital analysis, it can detect cases of leukocoria and automatically alert the parents for further investigation. In this study, the CRADLE detected leukocoria in the snaps captured before diagnosis by 1.3 years, for the majority of cases with ocular diseases (80%). The estimated sensitivity of the application was increased and the specificity was decreased with age. The CRADLE could provide to parents a useful tool for early detection of leukocoria. However, it was not able to differentiate the pathological for the physiological leukocoria due to specific conditions during photo shooting, and it definitely could not replace clinical evaluation with RRT and further examination. The researchers underlined that although pathological white pupils are usually signs of refractive errors or amblyopia and physiological leukocoria is a typical artifact of off-axis photography; recurrent white pupils in many photos are red flags. However, they made it clear that all cases of leukocoria in photographs should be investigated. More studies on these new technologies could empower the contribution of the RRT in diagnosing certain ocular pathologies of the pediatric population in the future.

DISCUSSION

RRT is a non-invasive, low-cost, essential diagnostic method, highly effective for the detection of several sight and life threatening ocular diseases. Its importance has been highlighted in 2016 by the AAP, American Association for Pediatric Ophthalmology and Strabismus, American Academy of Ophthalmology and American Association of Certified Orthoptists who published the revised policy statement on “Visual System Assessment in Infants, Children, and Young Adults by Pediatricians”[37]. The policy recommended that RRT should be performed at every pediatrician visit for newborns and infants 0-6 mo and again at 6 mo, 12 mo, 1-3 years, 4-5 years and 6 years. Furthermore, it has been emphasized that cases with abnormal findings or with history of prematurity or family history of congenital cataracts, retinoblastoma,

metabolic disease or systemic diseases with suspicion of severe ocular disorders must be referred to the ophthalmologist immediately[37].

Despite its clinical importance, literature research revealed that there is heterogeneity worldwide, regarding current recommendations for RRT implementation. Indicatively, some of the different strategies of European countries are hereby presented. In the United Kingdom, healthy infants should be examined for red reflexes during the first 3 d of life and again between 6-8 wk[47]. In Germany, the guidelines require repeated RRT at the ages of 4, 6, 12 and 24 mo. In Sweden, RRT is performed at birth and again at 4-6 wk[48]. In Greece, RRT is recommended at birth, at the age of 1-2 wk, 2 mo, 3-36 mo, and 36 mo-7 years[49]. Denmark and the recommendations by WHO do not include RRT in the pediatric vision screening but rather pencil light examination[38,50]. Remarkably, data from literature supported that RRT could never be replaced by pencil light examination, as the second tool seemed to be able to detect only advanced cases of cataract and retinoblastoma[17,38]. In Australia, each state and territory health department provides separate guidelines for pediatric vision screening. Most of the better quality guidelines recommended red reflex examination during newborn to 6 mo of age and later in the following years (from 18 mo to 3.5 years of age)[51]. The literature provides a little information about RRT recommendations in Asia and Africa. However, many countries, such as China and middle-low income countries, do not include RRT in the vision screening programs. The main reason may be the increased cost of eye examination from infancy[52].

Despite its clinical value, the RRT is not implemented by the entire pediatric community appropriately, as it is recommended. In order to improve the pediatricians' awareness and compliance with the current guidelines, prompt emphasis should be placed on the educational procedure of the physicians starting from university programs and during the years of pediatrics training. In this context, some researchers even suggested education videos on the internet[23,39]. The fact that many relevant articles are published only in ophthalmologic and not pediatric journals could be an obstacle for the pediatricians' awareness on RRT. Indicatively, 20 of the eligible articles for this review were available in pediatric journals, while the rest of them were published in non-pediatric journals.

The majority of the eligible articles of this review highlighted the importance of the RRT technique in the detection of certain pathologies (Table 3). On the other hand, Munson *et al*[46] considered the RRT as "dying art", since they focused on the limitations of the technique that have been described previously. However, the contribution of RRT in pediatric visual screening could be more promising in the future. New technologies based on red reflex may improve RRT's weak points[38,45,53]. Further investigation of these new devices and development of appropriate software is required in order to improve RRT accuracy on pediatric ocular diagnosis.

CONCLUSION

The present paper attempts to provide an updated review of the red reflex examination for the pediatrician. Published research indicates that the RRT should begin at birth and afterwards it should be an essential part of the routine clinical examination by pediatricians. Its simplicity and high sensitivity and specificity suggest that RRT should be part of the educational curriculum for every new pediatrician, since it will contribute to prompt diagnosis of many sight and life threatening conditions.

ARTICLE HIGHLIGHTS

Research background

Red eye reflex test (RRT) is a widely known examination that has been used by clinicians for the diagnosis of several ocular disorders. However, its implementation by pediatricians in the clinical practice still remains controversial. This study aims to highlight the importance of RRT and to provide a practical guide for its usage for pediatricians.

Research motivation

The literature data show insufficient implementation of the RRT. This result is in accordance with clinical observation in our country. Therefore, the present study could

contribute to raise pediatricians' awareness on this diagnostic tool.

Research objectives

The main objectives of the present study were the assessment of RRT value in specific disorders (such as retinoblastoma and congenital cataract) and the compliance of the clinicians with current guidelines. Moreover, this article investigated reported limitations of this diagnostic technique and motivated future research for the improvement of this method through new technological achievements.

Research methods

A thorough search on PubMed databases took place by two independent reviewers.

Research results

Eligible articles highlighted the significance of the RRT in the diagnosis of sight threatening or even life threatening eye pathologies. The implementation rates seemed to present a wide range among the countries. This fact, underlines the need for appropriate education and official guidelines from health systems.

Research conclusions

This study demonstrates why pediatricians should include the RRT in their clinical practice and provides a practical guide for the prompt implementation of this diagnostic examination. Further investigations are in progress in order to overcome the main limitations of the traditional red reflex examination.

Research perspectives

The rapid progress of technology achievements should improve the usage of the traditional red reflex method, making it easier and more efficient.

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