PREMATURES RETINOPATHY: 15-YEAR SCREENING FINDINGS IN A TUNISIAN NEONATAL UNIT

LA RETINOPATHIE DU PREMATURE : RESULTATS APRES 15ANS DE DEPISTAGE DANS UN CENTRE TUNISIEN

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Abstract

Retinopathy of prematurity (ROP) is an avoidable blindness cause. Our aim is to present and analyze our screening program. This was a prospective study of premature infants screened in Sfax neonatology's department (2005–2020). Were included: preterm<32 weeks of gestation (GW) and/or with birth weight<1500grams and preterm<34GW with a risk factor. The affected infants were followed and treated according to the ROP stage. Results: 3644 preterms were examined. Mean term was 30GW. The mean duration of oxygen therapy was 12 days [2-57 days].Twelve ROPs were diagnosed. The incidence was 0,22%. ROP was classified: 5 StageV, 3 StageIII, 2 StageII and 2 StageI. The treatment was surgical in stage IV ROP. Cryotherapy was used in stage III and stage II ROP. StageI ROP was treated successfully by argon laser photocoagulation. Conclusion: our screening program showed a decrease in ROP incidence since the department renovation. Earlier diagnosis and management are required to improve the prognosis.

Key-words: Screening; Premature retinopathy; Treatment.

Résumé

La rétinopathie du prématuré est l'une des principales causes évitables de cécité infantile. Notre but est de présenter et analyser les résultats du dépistage de ROP. Il s'agit d'une étude prospective dans le service de néonatologie de Sfax (2005-2020). Le dépistage concernait des prématurés<32 SA et/ou de poids de naissance<1500 grammes et des prématurés<34SA avec un facteur de risque. Les bébés atteints étaient suivis et traités en fonction du stade de ROP. Résultats: 3644 prématurés ont été examinés. La durée moyenne de l'oxygénothérapie était 12 jours. Douze ROP ont été objectivées. L'incidence était de 0,22 %. La ROP a été classée : 5 stade V, 3 stade III, 2 stade II et 2stade I. Le traitement était chirurgical au stade IV, cryothérapie en stade III et II, avec succès de la photocoagulation au laser argon au stade I. Conclusion : Notre programme de dépistage a baissé l'incidence de la ROP depuis la rénovation du service. La précocité du diagnostic et du traitement est indispensable pour améliorer le pronostic.

Mots - clés: Dépistage ; Rétinopathie du prematuré ; Traitement.

ملخص

اعتلال شبكية الخدج هو السبب الرئيسي الذي يمكن الوقاية منه لعمى الطفولة. هدفنا هو تقديم وتحليل نتائج تقصي، والذي كان محور دراسة مستقبلية بقسم أمراض الخدج بالمستشفى الجامعي الهادي شاكر بصفاقس لحديثي الولادة (2005-2020). كان الفحص مبكرا للخدج أقل من 32اسبوع ضهوي و/أو أقل من وزن 1500جرام والخدج أقل من 34 أسبوع ضهوي مع عامل خطر. تمت مراقبة الأطفال المصابين وعلاجهم بناءً على مرحلة الإصابة. وزن . تم فحص 3644 خدج. كان متوسط مدة العلاج بالأكسجين 12 يومًا. تم تجسيد12 حالة. أما نسبة الوقوع فهي 22 بالمائة. تم تصنيف الإصابة 5 على أنها المرحلة الخامسة و3المرحلة الثالثة و2المرحلة الثانية و2المرحلة الأولى. كان العلاج جراحيًا في المرحلة الرابعة، والعلاج بالتبريد في المرحلة الثالثة والثانية، مع تخثر ضوئي ناجح بالليزر الأرغون في المرحلة الأولى.التبكير في التشخيص والعلاج ضروري لتحسين التشخيص.

الكلمات المفاتيح : فحص مبكر ;اعتلال الشبكية للخدج; علاج

INTRODUCTION

Retinopathy of the prematurity (ROP) is a complication of prematurity. The incidence increases with the survival of extremely premature newborns especially in developed countries. It is a leadingcurable cause of childhood blindness worldwide (6 to 20% of childhood blindness) (1). An effective screening of this pathology improves its outcome. In our unit we started screening for retinopathy of the prematurity in year 2005. The aim of our study is to present and analyze the results of our screening program after15 years of screening program.

MATERIAL AND METHODS

This study is a prospective follow-up of premature infant who were examined for retinopathy of prematurity and were born between January 2005 and December 2020.

The screening concerned :

- all newborns with gestational age at birth ≤ 34 weeks and/or weight birth ≤ 1500 grams
- all newborns with gestational age at birth ≤36weeks and presenting at least one of this following risk factors:
    - prolonged oxygen therapy >72 hours
    - surfactant administration or blood transfusion administration
    - severe sepsis
    - multiple births
    - repeated apnea
    - hemodynamic disorders

These selection criteria were revised in 2008 and since screening concerned:

- all newborns with gestational age at birth ≤ 32 weeks and/or weight birth ≤ 1500 grams
- all newborns with gestational age at birth ≤ 34weeks and presented at least with one of the risksfactors cited above.

The screening modalities:

The fundus exam was performed by a single voluntary ophthalmologist at an average of seven exams/week. It was performed in the neonatology department, every Thursday, without any anesthesia.

- The first fundus exam was realized at four weeks after birth (+/- 6 days) or at 32 weeks (+/- 6 days) of postconceptional age if the infant was born at a gestational age ≤ 28 weeks.
- The fundus exam was then repeated every two weeks, two to three times until 40 weeks of postconceptional age if the infant was born at a gestational age ≤ 28 weeks.
- The affected infants were followed and treated according to their stage of ROP.

ROP classification :

considered was established by the international committee for the classification of retinopathy of prematurity (2005) (2) :

Stage 1: Demarcation Line**:** This line is thin and flat (in the retina plane) and separates the avascular retina anteriorly from the vascularized retina posteriorly.

Stage 2: Ridge: The ridge arises from the demarcation and extends above the plane of the retina. Small isolated tufts of neovascular tissue lying on the surface of the retina, may be seen posterior to this ridge structure.

Stage 3: Extraretinal Fibrovascular Proliferation**:** Intravitreal neovascularization or that which extends from the ridge into the vitreous. This extraretinal proliferating tissue is continuous with the posterior aspect of the ridge.

Stage 4: Partial Retinal Detachment**:** Retinal detachments usually begin at the point of fibrovascular attachment to the vascularized retina and the extent of detachment depends on the amount of neovascularization present.

Stage 5: Total Retinal Detachment**.**
More than one stage may be present in the same eye, staging for the eye as a whole is determined by the most severe stage present.

The fundus exam modalities:

- The fundus exam was realized after a feed.
- Pupils were dilated using 0.5% tropicamideor0.5% tropicamideassociated to 2.5% phenylephrine instilled three times at an interval of 15 minutes during 45 minutes
- The fundus was examined with a binocular indirect ophthalmoscope and +20 D lens.
- An antiseptic drop was instilled by the end of the exam.
- The results were noted on the medical record of the infant as well as on his medical report card.

RESULTS

During the study period, the screening for retinopathy of prematurity had concerned 3644 surviving newborns at risk, which makes an

average of 243 newborn at risk/year. Twelve infants had developed a retinopathy of prematurity given an incidence of 0, 22% of newborns at risk. Among these infants, five were diagnosed in year 2005.Mean gestational age was 30 weeks of gestation (GW) +3 days (extremes: 26 to 33GW). Mean birth weight was 1425 grams (extremes: 970 to 2050 grams). Among these 12 infants, 8 were male. Six were multiple births: all twins. Only one twin of each pregnancy had retinopathy of prematurity.

Maternal preeclampsia was present in two cases and a premature rupture of membranes in three other cases. Antenatal corticosteroids for lung maturation were administrated to only 8 mothers.

Delivery was vaginal in 4 cases. The APGAR score at the first minute of life was ≤ 7 in five cases requiring resuscitation in the delivery room.

All newborns were hospitalized for respiratory distress. Seven had required artificial ventilation and six surfactant administration. Mean duration of artificial ventilation was 8,4 days and it exceeded 5 days in 4 cases. The mean duration of oxygen therapy was12 days and it exceeded 5 days in 9 cases. Severe or repeated apnea was seen in five cases. Seven newborns had developed a severe sepsis associated to hemodynamic disorders. Blood transfusion was given to four infants. Seven newborns had developed a healthcare associated infection and three babies had developed an intraventricular hemorrhage.

The mean delay diagnosis was 10 weeks (4 to 21 weeks). The retinopathy of prematurity was classified stage V in five cases: three in 2005, one in 2012 and another one in 2017. The diagnosis was too late for these last two patients because they were rehospitalized several times in a pediatric intensive care for severe bronchiolitis.

The ROP was stage III in 3 cases, stage II in 2 cases and stage I in 2 cases. One of the stage III ROP cases progressed to a stage IV and another to a stage V(case in 2020) due to a delay in treatment because of the confinement during the COVID 19 pandemic.

For stage V, no treatment was proposed given the definitive vision loss. The stage I ROP was treated successfully with argon laser photocoagulation. The treatment was surgical in stage IV ROP. It was based on cryotherapy in stage III and stage II ROP. Cryotherapy was unsuccessful for one patient and a vitrectomy dissection was indicated. The remaining infants (stage IV and stage III ROP) were treated unsuccessfully with surgery. Lesions worsened for the stage III and IV ROP as management was delayed (mean delay treatment after diagnosis was 9 weeks (1 to 32 weeks)). Thus, the outcome was blindness for 6 infants and impaired vision for 2 infants (Table1).

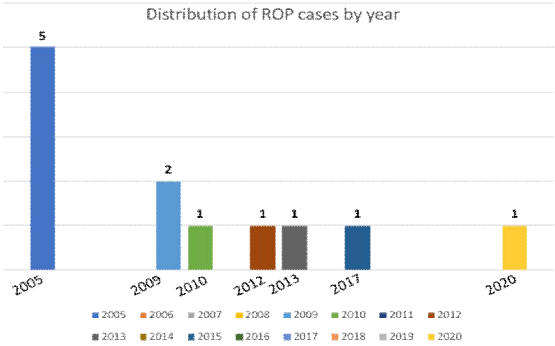

Figure 1: Distribution of the newborns with retinopathy of the prematurity (ROP) by year

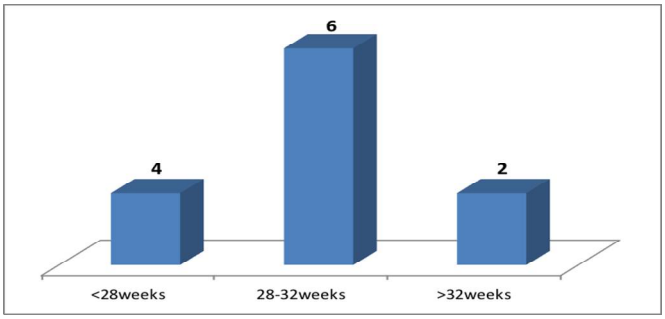

Figure 2: Distribution of the newborns with retinopathy of the prematurity according to their gestational age

Table 1: characteristics of the twelve cases of retinopathy of prematurity

Year	Gender	Multiple birth	Antenatal Corticosteroid therapy	Term	Delivery	Birth weight	Oxygen duration	Artificial ventilation duration	Surfactant given	Comorbidity	ROP stage	Treatment	Outcome
2020	Female	yes	yes	27 weeks	c-section	970g	56days	5 days	Yes	Noso infection HIV Blood transfusion	Stage III Progresse d V	No	blindness
2017	Female	No	No	28 weeks	c-section	900g	15days	3 days	Yes	Noso infection	Stage V	No	blindness
2013	Male	Yes	Yes	30 weeks	c-section	1420g	15 days	11 days	Yes	Noso infection HDD Blood transfusion	Stage I	Argon laser	
2012	Male	Yes	No	33 weeks	c-section	2050g	9 days	7 days	No	Apnea	Stage V	Surgery	Impaired vision
2010	Female	No	Yes	31 weeks	c-section	1100g	14hours	-	No	Noso infection HDD	Scaring forme	No	Impaired vision
2009	Male	No	Yes	33 weeks	c-section	1900g	8 days	1 day	Yes	Noso infection HDD + IVH	Stage III	Cryotherapy	blindness
2009	Male	Yes	Yes	31weeks	c-section	1470g	7 days	2 days	Yes	Noso infection HD	stageIV	Cryotherapy	Impaired vision
2005	Male	Yes	No	29 weeks +5 days	vaginal	1650g	19 days	19 days	Yes	Noso infection HDD+ IVH Blood transfusion	Stage V	No	Impaired vision
2005	Male	Yes	Yes	31 weeks	vaginal	1000g	2 days	0	No	Apnea Blood transfusion	Stage V	No	blindness
2005	Male	No	No	26 weeks	vaginal	1020g	2days	0	No	Apnea Noso infection HDD	Stage III	Surgery (at stage IV)	blindness
2005	Male	No	Yes	31weeks	vaginal	1620g	16 days	9 days	Yes	_	Scarring form	No	Impaired vision
2005	Female	No	Yes	27 weeks	vaginal	1150g	7 days	0	No	Apnea	Stage VI	No	blindness

DISCUSSION

Our ROP screening program began in 2005 and we here report its first results. There are no other national results already published. The ROP incidence in our unit was 0,22% after a screening of 3644 premature infants until 2020. Several risk factors were identified, but a delay in diagnosis and management of some patients was also responsible for their visual impairment.

The reported findings concerning the incidence of ROP and its severity are varying and even controversial. The reported incidence of ROP varies from 0,17% (global incidence) to89% (incidence in newborns with gestational age < 27 GW) [1-5]. In a Turkish study similar to our's, managed in a tertiary neonatal intensive care unit, on a population of 330 preterm gestational age ≤ 34 weeks screened between September 2005 and July 2009, the ROP incidence was 32.1% [6]. In another French study including 94 screened newborns with gestational age < 32 weeks or with birth weight < 1500 g in year 2002 the incidence of ROP was 22,3% [7]. The low incidence found in our study (0,22%) could be explained by the fact that the mortality rate is still high among the newborns at risk, especially that in our unit we opt for no aggressive therapy for newborns with gestational age under 28 weeks or birth weight under 1000g. In addition, many factors may influence the study's results: the development level of the unit, the existence or not of an effective screening and treatment program, the type of the study and the considered criteria (gestational age, the ROP stage…). This makes findings hardly comparable.

In most developed countries, infants with gestational age > 32 weeks and birth weight > 1500 g are not screened. In our study, 2 infants who had a stage III and V ROP were born at 33 weeks gestational age and their birth weight was> 1500g (1900 and 2050g respectively). These two newborns would have been missed if we had used the criteria of developed countries for screening. It seems then reasonable to set criteria for ROP screening programs according to local conditions. In fact, in developed countries, the situation seems to be different from developing ones where ROP is concerning more mature infant [2,8]. This could be explained by the fact that in developing countries other risk factors in addition to low gestational age and low birth weight interfere, especially severe sepsis, nosocomial infections, poor management of severe respiratory distress syndrome, lack of monitoring, poor management of apnea etc….

Recent studies showed that ROP is rather a multifactorial disease. It implicates both oxygen-dependant (including oxygen stress) and oxygen-independent (including deficit in growth factor) mechanisms [1,2,9]. Several conditions or stimuli can lead to these pathogenic mechanisms and many studies have investigated risk factors of ROP. The most reported were low gestational age, low birth weight, respiratory distress syndrome, apnea, duration of artificial ventilation, intraventricular hemorrhage, sepsis, blood transfusion and prolonged parenteral nutrition [6]. Our study did not assess risk factors of this pathology because our sample was not statistically representative. However, we noticed that some factors were rather common in our infant especially respiratory distress syndrome (all infants), duration of artificial ventilation (7/12 infants), apnea (5/12 infants), sepsis and hemodynamic disorders (7/12 infants). Indeed, the risk of ROP persists beyond the first month of life if the newborn is still exposed to the oxygen. In our study, two infants who had a stage V were rehospitalized for severe bronchiolitis.

The decrease of ROP incidence after year 2005 can be explained by the improvement of care for newborns with low gestational age and low birth weight, thanks to the renovation of our unit in 2007. The introduction of new Continuous Positive Airway Pressure (CPAP) devices as well as a device for the measurement of blood gases allowed us a more precise and controlled oxygen administration with a better control of blood pressure and oxygen fluctuations which are known to be implicated in the pathogenesis of ROP. The introduction of CPAP has also enabled us in combination with caffeine use to improve the management of apnea of prematurity and reduce hypoxic episodes they induce. In addition, the availability of new incubators, new syringes and electric pumps permitted a better controlled parenteral support and then improved the management of newborn premature and low birth weight as evidenced by the decrease in the mortality of children under 32 GW.

The incidence of severe injury and poor outcome especially in the first year of the study could be explained by a still limited specialized management of this disease in our country (photocoagulation treatment Laser Argon was introduced in 2012 and only in private clinics), but also a delayed diagnosis at an advanced stage despite the screening program. The mean delay diagnosis was 10 weeks (4 to 21 weeks). Two infants had missed their first exam and their pupils were poorly dilated in the

second exam. For the others the fundus exams were delayed because of the lack of availability of appointments, not only because there was a single ophthalmologist, but also because of the wide selection criteria. This has prompted us to revise our selection criteria in year 2008 considering the new U.S recommendations (≤ 30 weeks gestational age or birth weight <1500 g) [10] and the new British recommendations (gestational age ≤ 31 weeks or birth weight ≤ 1500 g) [11].

It is clear that our screening and prevention strategy is successful; however, the evolution of both the diagnosis and classification of rheumatoid arthritis and its management must be taken into consideration. In fact, a third revision of the International Classification of Retinopathy of Prematurity, was published in 2021 [12]. This revision was required because of challenges such as: concerns about subjectivity in critical elements of disease classification; innovations in ophthalmic imaging; novel pharmacologic therapies such as anti-vascular endothelial growth factor agents (anti-VEGF) [13] with unique regression and reactivation features after treatment compared with ablative therapies; and recognition that patterns of ROP in some regions of the world do not fit neatly into the current classification system [12].

Major updates in the ICROP3 include refined classification metrics (e.g., posterior zone II, notch, subcategorization of stage 5, and recognition that a continuous spectrum of vascular abnormality exists from normal to plus disease). Updates also include the definition of aggressive ROP to replace aggressive-posterior ROP because of increasing recognition that aggressive disease may occur in larger preterm infants and beyond the posterior retina, particularly in regions of the world with limited resources. ROP regression and reactivation are described in detail, with additional description of long-term sequelae [12].

CONCLUSION

The incidence of ROP decreased after 2005 thanks to the renovation of our intensive care unit. To improve the visual outcome of children at risk, it is imperative to improve the early care by training other specialists for screening, the introduction of new screening equipment especially RetCam, and the introduction of new therapies especially Argon Laser and anti-VEGF drugs most recently emerged as a favorable treatment option for zone-I and II ROP.

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