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ORIGINAL ARTICLE

RETINOPATHY OF PREMATURITY - AN EMERGING CAUSE OF CHILDHOOD BLINDNESS IN ETHIOPIA

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ABSTRACT

Introduction: *Retinopathy of prematurity is an increasing cause of blindness in children in low income countries as neonatal services expand.*
Objective: *To describe the characteristics, stage of retinopathy of prematurity and treatment outcomes in preterm infants attending a tertiary eye center.*
Methods: *Review of medical records from June 2016 to December 2019. Data on birthweight, gestational age, postmenstrual age at presentation, age at first examination, stage of retinopathy of prematurity , and treatment outcomes were extracted and analysed.*
Results: *Thirty three of 93 (35.5%) infants had retinopathy of prematurity : vision-threatening 21 (22.6%); two with aggressive posterior retinopathy of prematurity, or Stage 4/5 (n=12). The mean (±SD) gestational age of these 33 infants was 29.1 (±1.9) (range 26-33) weeks; mean (±SD) birth weight was 1185.6 (±234.5) (range 680–1800)g. Treatments were: anti-VEGF injection (n=6), LASER (n=1), anti-VEGF and LASER (n=1), lens-sparing vitrectomy (n=1), lensectomy with vitrectomy (n=1), LASER and lensectomy with vitrectomy (n=1). In 18 cases retinopathy of prematurity regressed (11 spontaneously, 7after treatment), and one failed follow up. One progressed to stage 4 and 12 (10/93, 12.9%) were blind or visually impaired.*
Conclusions: *Preterm infants at risk of retinopathy of prematurity are now surviving in Ethiopia. There is a need to increase awareness and establish retinopathy of prematurity screening and treatment services, with wide screening criteria initially to determine the population at risk of vision threatening retinopathy of prematurity .*
Key words: *Preterm birth, low birth weight, Retinopathy of prematurity, childhood blindness, Ethiopia.*

INTRODUCTION

Retinopathy of prematurity (ROP) is a vision-threatening disease associated with abnormal retinal vascular development at the boundary of vascularized and avascular peripheral retina of preterm babies (1). The main risk factors for ROP are prematurity, low birth weight and hyperoxia from poorly regulated use of supplemental oxygen (2, 3). The first case reports of retrolental fibroplasia, as ROP was called then, were described by Terry in Boston, in the United States of America in 1942 (4).

Since then ROP has become a leading cause of avoidable blindness in children in most regions of the world. The World Health Organization's Vision 2020 initiative, which was launched in 1997, identified ROP as an important emerging cause of blindness in children, particularly in the middle-income countries of Latin America, Eastern Europe, and Asia (5). In 2010 it is was estimated that every year 32,300 preterm infants become blind or visually impaired (1).

More than 60% of the world's 15 million preterm births occur in South Asia and Sub-Saharan Africa (6). Until recently there were limited data regarding the incidence of ROP in Africa. However, in the last decade, there has been an increasing number of published reports which show that ROP is emerging in some African countries. ROP screening guidelines are in place for only two countries in Africa (South Africa and Kenya)(7), yet the systematic review by Wang D *et al* showed that there are published data on ROP from six African countries including South Africa, Egypt, Nigeria, Sudan, Rwanda and Kenya(8).

There have been three epidemics of blindness due to ROP since it was first described in the 1940s (9). The first two occurred in high income countries (USA and Western Europe): the first epidemic was due to the use of unmonitored 100% supplemental oxygen, and the second was due to greater survival of increasingly preterm infants.

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The third epidemic of ROP began in the 1990s in the middle income countries of Eastern Europe, Latin America and South East Asia due to the increased survival of premature infants as a result of expansion of intensive neonatal care services (10). However, neonatal care was often of inadequate quality, and coverage of ROP screening and treatment services was low (7,9).

The third epidemic has already started in South Africa, an upper middle income country, and other countries in the region are considered to be the next frontier for ROP epidemics as a result of increasing economic development and expanding neonatal care (7).

Ethiopia, the second most populous nation in Africa, has a preterm (<37 weeks of gestation) birth rate of 10% and a low birth weight rate (babies born <2,500g) of 20%. Every year 320,000 babies are born preterm (11). The two previous studies in schools for the blind in Ethiopia (published in 2003 and 2017) reported no cases of ROP blind children at that time (12, 13). However, Wang D *et al* in their review postulated that there are a number of populous countries with comparable health systems to those for whom there are published data in Africa, where it is likely that ROP will emerge, such as Ethiopia, Democratic Republic of Congo, and Tanzania (8).

In this study we report a series of preterm infants with ROP for the first time in Ethiopia, and the outcomes of treatment. The infants were all examined in a private tertiary eye center in Addis Ababa, Ethiopia.

PATIENTS AND METHODS

A center-based, retrospective review of records was undertaken of all premature infants who attended the WGGA eye center between June 1, 2016 and December 31, 2019. The study protocol was approved by WGGA eye center ethics review committee. Data were extracted from the electronic medical records using a pre-designed check list, including mode of referral, birthweight (BW), gestational age (GA), postmenstrual age (PMA) at presentation, postnatal age at first examination, the number of days on oxygen, diagnosis and stage of ROP, method of treatment if required, and treatment outcomes. Data were entered into Microsoft Excel, and exported into and analyzed using Epi info 7 software.

Examination was conducted immediately on arrival at the outpatient pediatric ophthalmology and strabismus clinic. All infants were examined for ROP by one pediatric ophthalmologist initially (MA), and those with a diagnosis of ROP were also examined by a retina specialist (AK). Pupillary dilatation was achieved using a mydratic cocktail of 0.5% cyclopentolate and 2.5% phenylephrine or 1% tropicamide plus 2.5% phenylephrine instilled three times every 5-10 minutes. After instillation of topical anesthesia (0.5% proparacine hydrochloride ophthalmic solution), an Alfonso newborn eyelid speculum was inserted, and a Flynn scleral depressor was used to rotate the eye. Funduscopic examination was by indirect ophthalmoscopy (Keeler Spectra Iris) using a 28D Volk© lens. Retinal changes were classified according to the most advanced stage of ROP using the International Classification of ROP (14).

If vascularization was incomplete, infants were seen at 2-weekly intervals until mature retinal vessels were confirmed, or ROP developed. Infants with ROP were seen at weekly intervals until regression or Type 1 ROP was noted. Type 1 ROP was defined as any stage of ROP in zone I with plus disease; zone I, stage 3 ROP without plus disease; or zone II, stage 2 or 3 ROP with plus disease (15). Those with Type 1 ROP received either confluent LASER peripheral photocoagulation to the avascular retina or anti-vascular endothelial growth factor (VEGF) (Avastin, Lucentis or Eylea) injection within 48 hours of diagnosis. Those with Type 2 ROP (Stage 1-2 without plus disease in zone I, Stage 2-3 without plus disease in zone II) were followed up weekly until regression of ROP or until vascularization into zone III was achieved. Lens sparing vitrectomy or lensectomy and vitrectomy surgery were performed for stage 4 and selected cases of stage 5 ROP.

RESULTS

Ninety-three preterm infants were included in the study; 53 (57%) were female and 17 (18.3%) were from multiple births. Most infants (87.1%) were referred for ROP screening by pediatricians from three private neonatal units. Two infants with stage 4 ROP were referred for treatment by an ophthalmologist from a government university hospital. The remaining 10 cases were brought by parents seeking a solution for the abnormal visual behavior they had noticed in their child (Table 1).

The mean (±SD) GA was 30.9 (± 2.5)(range 26-40) weeks and the mean (±SD) BW was 1500.2 (± 491.7) (range 680-3900) gram. Mean (±SD) age at first examination was 10.3 (±15.4) (range 2 -116) weeks and the mean (±SD) PMA (GA plus chronological age) was 40 (±9.3) (range 31 -90) weeks.

Table 1: Characteristics of infants with retinopathy of prematurity presenting to WGGA Eye Center, Addis Ababa, Ethiopia, from June 2016 to December 2019 (N =33)

						Eye with most advanced ROP				
	How referred	**GA**	**BW**	**Days in oxygen**	**PMA at presentation (weeks)**	**Stage**	**Zone**	**Plus**	**Treatment**	**Outcome**
1	Self	26	ND	ND	90	5			None	Blind
2	Self	26	1200	ND	62	5			None	Blind
3	Self	30	900	30	55	5			None	Blind
4	Self	29	1350	32	57	5			None	Blind
5	Self	28	1150	ND	68	5			None	Blind
6	Self	28	1000	30	56	5			None	Blind
7	Self	28	1400	ND	60	5			None	Blind
8	Self	29	1100	ND	53	4			None	Blind
9	Self	27	1300	54	59	5			None	Blind
10	Self	ND	ND	ND	ND	5			None	Blind
11	Ophthalmologist	32	1800	12	48	4			PPV	VI
12	Ophthalmologist	28	1000	60	44	5			PPV/lensectomy	VI
13	Pediatrician	27	1130	56	35	3	1	Yes	Laser/PPV/ lensectomy	Progressed to Stage 4, VI
14	Pediatrician	27	1400	14	32	APROP	-	Yes	Avastin	Regressed
15	Pediatrician	32	1070	15	36	APROP	-	Yes	Lucentis	Regressed
16	Pediatrician	29	1000	63	53	3	2	Yes	Avastin	Regressed
17	Pediatrician	27	680	77	40	3	2	Yes	Laser	Regressed
18	Pediatrician	31	1350	25	34	3	2	No	Avastin	Regressed
19	Pediatrician	30	1300	30	35	3	2	Yes	Avastin	No follow up
20	Pediatrician	28	1080	35	33	3	2	Yes	Avastin	Regressed
21	Pediatrician	29	1100	30	38	3	2	Yes	Eylea	Regressed
22	Pediatrician	27	1180	ND	63	2	2	No	None	Regressed
23	Pediatrician	30	1400	0	36	2	2	No	None	Regressed
24	Pediatrician	30	1300	35	36	2	2	No	None	Regressed
25	Pediatrician	31	1300	30	37	2	2	No	None	Regressed
26	Pediatrician	31	1040	28	36	2	2	No	None	Regressed
27	Pediatrician	29	2038	33	40	3	3	No	None	Regressed
28	Pediatrician	33	1800	9	36	2	2	No	None	Regressed
29	Pediatrician	29	1200	20	43	3	2	No	None	Regressed
30	Pediatrician	30	1100	7	34	1	2	No	None	Regressed
31	Pediatrician	29	900	60	ND	1	3	No	None	Regressed
32	Pediatrician	26	1000	35	31	2	2	No	None	Regressed
33	Pediatrician	31	1185	25	36	2	2	No	None	Regressed

ND = no data; APROP =Aggressive posterior ROP; PPV= pars plana vitrectomy; VI =visually impaired; PMA = Postmenstrual age

Among infants referred by a pediatrician for ROP screening (n=81), the mean (±SD) age at examination was 6 (± 4.9) (range 2 – 36) weeks and mean (±SD) PMA was 37.2 (± 4.2) (range 31-63) weeks. Fifty-five babies (55/81, 62.9%) were examined between 25 – 40 days of age. Twenty-one of these 81 infants (25.9%) developed ROP and ten (12.3%) needed treatment. The mean (±SD) age at examination for self-referred cases was much higher [42.0 (±28.7), range 20 -116 weeks] than those referred by pediatrician ($\chi 2$ =102.1, p <0.001). Among the 93 infants included in the study, 33 (33/93, 35.5%) were diagnosed with ROP, 21 of whom (21/93, 22.6%) had vision-threatening and 12 (12.9%) had mild ROP.

The mean (±SD) GA of these 33 infants was 29.1 (±1.9) (range 26-33) weeks; mean (±SD) BW was 1185.6 (±234.5) (range 680–1800) gram. Twenty-one infants (22.6%) had vision threatening ROP (i.e., any Zone I disease (n=1), Stage 2 or 3 disease in Zone II with plus disease (n=6), two had aggressive posterior ROP (APROP) and 12 had Stage 4 or 5 ROP). The mean GA of these 21 infants was 28.6 ± 1.8 (range 26 – 32) weeks, mean (±SD) BW was 1174.2 (± 239.4 (range 680-1800) grams, and the mean (±SD) PMA at presentation was 48.7 (±14.9) (range 32-90) weeks. Figure 1 shows the distribution of BW by GA for infants with vision threatening ROP, showing that all fell within the screening criteria used in the United Kingdom (GA of ≤32 weeks or BW <1501 grams) (16).

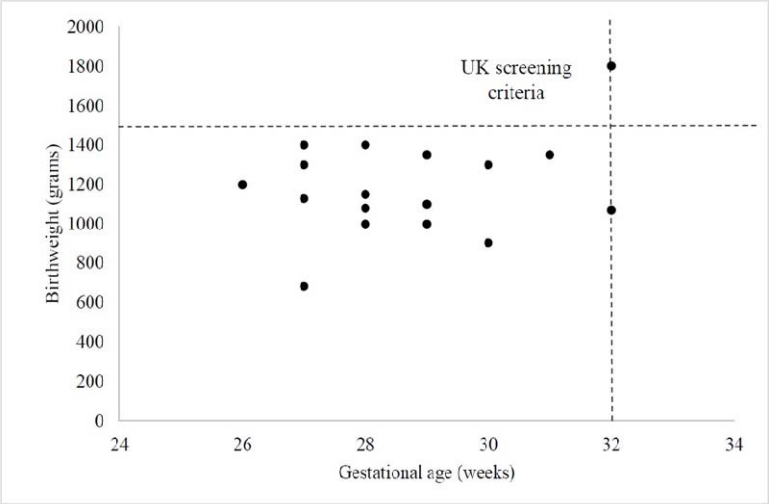

Figure 1: Gestational age and birth weight of infants with vision-threatening or Stage 4/5 ROP at WGGA Eye Center, Addis Ababa, Ethiopia (n=19; two with incomplete data).

Only 7 of the 93 (7.5%) infants did not receive oxygen, and data on the use of oxygen was not available for 10 (10.7%) cases. The mean (±SD) number of days on oxygen overall (76 infants) was 19.1 (±17.23) (range 1-77) days and was 37.5 days for infants with vision-threatening ROP, 28.2 days for those with ROP not requiring treatment, and 12.0 days for infants without ROP ($\chi 2$ =8.35, p=0.01).

Among infants with ROP, 11 (11/33, 33.3%) were treated as follows: anti-VEGF injection (n=6); peripheral LASER photocoagulation (n=1); anti-VEGF and laser (n=1); lens-sparing vitrectomy (n=1); lensectomy with vitrectomy (n=1); and LASER, then lensectomy with vitrectomy (n=1). In 18 cases (19.3%) ROP regressed (11 cases spontaneously and 7 after treatment), and one was lost to follow up. One case progressed to stage 4 despite treatment with LASER followed by pars plana vitrectomy. Twelve (12/93, 12.9%) infants were blind or visually impaired (Table 1). There was an increasing trend in the number of ROP cases: two in 2016, four in 2017, 12 in 2018, and 15 in 2019.

DISCUSSION

This study shows that preterm, very low birth weight infants are now surviving with ROP in Ethiopia. This is the result of several factors, including improved antenatal care, a higher proportion of hospital deliveries, and the recent establishment of neonatal intensive care units (NICUs) with trained neonatologists in many government and private hospitals in Addis Ababa. However, to the best of our knowledge ROP screening is not taking place in any of these units.

The finding that most cases were referred by paediatricians working in private NICUs suggests that there is some level of awareness of the need for ROP screening, at least in the private sector. However, babies were only referred from three units which may mean that the level of awareness is not uniform among all practicing paediatricians/ neonatologists in the city. Postnatal age at examination among referred cases ranged from 2 to 36 (mean 6) weeks and 62.9% were examined between 25 and 40 days of age which implies that a significant proportion of preterm babies were being referred and attended in a timely manner. In contrast, there was a marked delay in presentation among self -referred cases, as the mean age at examination was nearly one year (42 weeks), with one child presenting at over two years of age (116 weeks).

These infants had not been screened for ROP and were brought by their parents who had noticed “something white in the eyes” or a change in the visual behaviour of their child. Almost all the self-referred cases had end stage, inoperable ROP and were blind. Similar findings have been reported from Mexico, including late presentation among 48 ROP blind infants, where the median age at presentation was 5±2 (range 1-11) months (17).

In another study of 66 ROP blind infants attending a tertiary eye hospital in India, 52% were referred by an ophthalmologist and 30% were self-referred. 50% of these infants had received care in a neonatal unit without ROP screening services (18). Similar studies have not been reported from Africa.

In this study 35.5% of infants had ROP, 22.6% with vision-threatening disease, 33.3% needed treatment and 12.9% were blind. Our data cannot be directly compared to other studies in Africa where babies were all identified during screening in NICUs. In a retrospective study of screening in Kenya, 41.7% developed ROP, and 20.9% had vision-threatening disease (19). In a prospective study of 53 babies screened for ROP in Nigeria, 47.2 % developed ROP but only one developed threshold disease (20).

There is an urgent need to increase awareness and establish ROP screening and treatment services in Ethiopia. In our study no infant fell outside the United Kingdom screening criteria (16), but this may reflect selection bias, as infants may have received higher quality neonatal care in the private sector than they would have in government facilities. More studies are needed in government and private NICUs because, as in many low- and middle-income countries, larger, more mature infants may also be developing vision-threatening ROP in NICUs with less high-quality neonatal care (21). ROP screening guidelines must be locally relevant, as criteria which are appropriate in high income countries may not be applicable in low- and middle-income countries due to variation in exposure to risk factors (22). The screening criteria used in South Africa and Kenya are similar to those used in the UK, but in The Philippines, for example, the criteria are a GA of <35weeks or BW of <2000 grams (23).

A limitation of the study is that information on oxygen exposure was limited to days on oxygen, and this information came from parental recall or referral letters. The finding that the number of days on oxygen increased in line with the severity of ROP suggests that inadequately monitored supplemental oxygen may be a risk factor in this setting. Prospective studies are required, which should include awareness of the revised recommendations on optimal target oxygen saturation levels for preterm babies (90-94%), and the ability of staff in neonatal units to implement them (24).

In conclusion, this study indicates that preterm infants at risk of ROP are now surviving in Ethiopia. There is an urgent need to establish ROP screening and treatment services, to increase awareness among clinicians taking care of preterm babies and to build the capacity of ophthalmologists in screening and treatment. Although indirect ophthalmoscopic retinal examination is the standard for examining the retinae of infants, wide-field imaging for screening is gaining popularity. This is especially relevant in countries that lack ophthalmologists able to screen for ROP (25). Wide screening criteria should be used initially to delineate the population at risk of vision threatening ROP in this context. More studies on the prevalence and risk factors for ROP in NICUs are highly recommended.

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