

Treatment of acute retrolental fibroplasia by cryopexy

I. BEN-SIRA, I. NISSENKORN, E. GRUNWALD, AND Y. YASSUR

From the Department of Ophthalmology, Beilinson Medical Center, Tel-Aviv University Medical School, Petah-Tiqva, Israel

SUMMARY Fifteen to 20% of premature infants weighing below 1500 g develop variable degrees of acute retrolental fibroplasia (RLF). Approximately 5% of those infants who develop RLF can be expected to become blind. A prospective study was carried out to evaluate if early cryopexy can prevent this blindness. The study showed that, among 533 infants admitted to the neonatal intensive care unit between July 1976 and December 1978, 55 had some degree of active RLF. In 18 eyes of 9 infants in whom the retinopathy progressed beyond active stage II cryopexy treatment was applied to the avascular retina. In all the treated eyes the active retinopathy regressed, and there were no complications due to the procedure. The long-term follow-up showed that in 15 eyes there was good vision and that the remaining 3 eyes had some impairment of vision but were not blind. These results suggest that cryotherapy may prove useful in treating premature infants with RLF who show progression of their active stage, without the danger of further visual loss or complete blindness.

Retrolental fibroplasia (RLF) is still a persistent problem in spite of modern techniques of monitoring P_{aO_2} levels. Since both the incidence and the severity of RLF are directly related to the degree of prematurity as manifested by low birthweight (see Tables 1, 2), this disorder can be expected to become an even more serious problem with the increasing capability of preserving life in extremely small premature infants.

In the majority of infants with RLF there is a spontaneous regression of the active stages with a subsequent normal vision. It has been found, however, that about 5% will become totally blind due to cicatricial RLF (Table 2). In addition, a certain number, as yet undetermined, will show other serious ocular abnormalities such as high myopia, vitreous traction, dragged retinal vessels, heterotopic macula, strabismus, and amblyopia. Late complications include peripheral retinal degeneration, retinoschisis, retinal tears, and retinal detachment.

Several authors^{1–3} have worked out grading systems for the classification of the various stages of acute and cicatricial RLF. Others⁴ have provided more understanding of the pathogenesis of the disease by their report on the use of fluorescein

angiography and the clinicopathological correlations derived from it. There are, however, only a few recent reports on the incidence, prevalence, and natural history of this disease, especially in premature babies with RLF weighing below 1500 g at birth.

Since RLF has characteristics which are common to other ischaemic retinopathies, it was only natural that methods of treating such retinopathies, such as photocoagulation and cryopexy, would be tried in its treatment as well. Conflicting results have been obtained by this approach,^{5–12} probably owing to the lack of clear indications as to the optimal time of treatment and the exact method to be used.

In July 1976 a prospective study was started on premature babies with acute RLF to see whether blindness could be prevented by giving cryopexy treatment to selected eyes judged to have an increased probability of developing severe cicatricial RLF. The results of Kingham's series¹² encouraged us to report the preliminary results of this study even before data from controlled studies on large numbers of eyes are available, in order to demonstrate that cryopexy, if done early, may be not only harmless but better than no treatment or than treatment carried out only when the eyes reach active stage IV, as in Kingham's series.¹² The purpose of this report is also to stress the direct relationship between low birth weight and the

Correspondence to Dr Y Yassur, Department of Ophthalmology, Beilinson Medical Center, Petah-Tiqva, Israel.

Table 1 Incidence of active retrolental fibroplasia and birthweight

Reference	Total no. preterm infants	% with acute RLF	Birth weight (in grams)			
			500-1000 No. of RLF	1001-1500 No. of RLF	1501-2000 No. of RLF	2001-2500 No. of RLF
Kinsey <i>et al.</i> ¹⁴	719	10.6%	—	86 (36%)		
Johnson <i>et al.</i> ¹³	176	18%	8 (75%)	50 (32%)	52 (17%)	37 (5%)
Kingham ³	521	16%	Not reported			
Majima ¹⁷	470	32.6%	Not reported			
Present study	533	10%	31 (61%)	112 (20.5%)	209 (5.2%)	68 (1.5%)

Table 2 Severity of cicatricial RLF in relation to birth weight in previous studies

Reference	Total no. infants	No. of infants with active RLF	No. of eyes with cicatricial RLF from total infants	No. of eyes with cicatricial RLF grades I-II from infants with active RLF	Same for grade III	Same for grades IV-V	Infants below 1000 g	No. of eyes with cicatricial RLF from all infants below 1000 g	Comments
Kinsey <i>et al.</i> ¹⁴	719	66 (11%)**	27 (4%)	21 (32%)	3 (5%)	3 (5%)	86*	34 (20%)* 17 (20%)	*Under 1200 g birthweight. **10 cases excluded because of lack of data. 1971
Gunn <i>et al.</i> ¹⁵	?	?	—	—	2 (3%)	4 (11%)	18	4 (11%)	Data from 1962-71.
Lempert ¹⁸	185	8 (5%)	17 (5%)	12 (33%)*		4 (6%)	35	15 (43%)	Data from 1972-6
Johnson <i>et al.</i> ¹³	176	33 (19%)		19 (29%)		5 (14%)*	—		*Estimate based on 10% active RLF 1975
Shahinian and Malachowsky ¹⁹	375	12 (3%)	8 (11%)			2 (3%)	8		1968-71
						8 (11%)*			*Estimate based on 10% active RLF 1973-4

occurrence and severity of RLF, the absence of long-term complications due to the treatment, and the absence of any blindness in the treated eyes.

Materials and methods

All of the 533 surviving premature babies admitted to the neonatal Intensive Care Unit of the Beilinson Medical Center between July 1976 and December 1978 were examined. The first indirect ophthalmoscopic examination was usually carried out at the age of 2 weeks, with a subsequent monthly examination up to the age of 6 months. Acute retrolental fibroplasia was diagnosed in 55 infants (10%), who were then examined weekly. Eyes were considered to require treatment if serial examinations revealed progression of the retinopathy beyond active stage II according to Patz's classification.² In the initial stages of this study only the worse eye was treated. However, 2-6 weeks later, when it was evident that there was an arrest of the active retinopathy in the treated eye and that no

complication had occurred, the fellow eye was treated too, if it had also progressed beyond active stage II.

Cryopexy was performed under general anaesthesia with ketamine hydrochloride, with or without the use of an endotracheal tube. The conjunctiva was never incised and the muscles were never held by fixation forceps or fixation sutures. Under observation with an indirect ophthalmoscope a retinal cryoprobe was placed transconjunctivally over the peripheral avascular retina. The retina anterior to the neovascularisation tufts was treated, each location being frozen only once. No particular attempt was made to freeze the neovascular tufts themselves. No special postoperative treatment was applied.

Results

Among the 55 infants with active RLF the retinopathy never exceeded stage II in 46 (84%), and eventually spontaneously regressed and healed. All

the 9 infants in whom the active retinopathy started to progress beyond stage II and who were subjected to treatment weighed below 1500 g at birth. Three weighed between 1001 and 1500 and 6 weighed between 500 and 1000 g (Table 3). In these infants the temporal ridge was thick, and the neovascular

tufts were large and engorged. There was an elevated retinal neovascularisation and small to moderate vitreous haemorrhages. After ablative cryopexy over the avascular retina these 18 eyes showed a rapid arrest of the active retinopathy and started to heal.

No complications resulted from the cryoapplication. In all cases the slight conjunctival chemosis and lid swelling present postoperatively subsided within 2-3 days. None of the eyes progressed to more than cicatricial stage II. Fifteen of these treated eyes were later found to have macular fixation, and they were considered to have good vision. Of the other 3 eyes, 1 became highly myopic (case 7, Table 4) and 2 developed mildly displaced macula (case 1, Table 4).

Table 3 Incidence and severity of active RLF in relation to birthweight

Birthweight in g	No. of infants	Infants with acute RLF	Active RLF exceeding stage II treated cases	% of active RLF treated % of total no. of infants
500-1000	31	19 (61.3%)	6	32% 19%
1001-1500	112	23 (20.5%)	3	13% 3%
1501-2000	209	11 (5.2%)	—	—
2001-2500	68	1 (1.5%)	—	—
2500-	113	1 (0.9%)	—	—
Total	533	55 (10.3%)	9	16% 1.6%

Discussion

Only a few published reports provide precise data of the natural history of acute RLF (Table 2). It is generally accepted that the mild forms of RLF are reversible. It was noted in previous studies, as well as in ours, that the great majority of cases of acute RLF occur among infants of low birth weight, and that they are more severe.^{13 14}

Table 4 Relevant data on 18 eyes with retrolental fibroplasia

Case	Eye	Birth weight (g)	Days in oxygen	Max. PaO ₂	Age at diagnosis (weeks)	Shape of active RLF at diagnosis	Age at treatment (weeks)	Optic nerve angle*	Active RLF stage at treatment	Duration of follow-up	RLF stage cicatricial	Optic nerve angle	Comments	Ocular picture at last examination
1	OD	800	4	120	7	II	9	100°	III	72 weeks	II	70°	Good vision	Displaced macula
	75°							III	55°			4.5 sph. myop.		
2	OD	620	7	55	10	I	13	120°	II	63	I	100°	Good vision	Normal
	120°							III	90°					
3	OD	1080	8	64	12	I	15	120°	II-III	45	—	120°	Good vision	Normal
	120°							II-III	120°					
4	OD	980	7	170	6	I	10	100°	III-IV	41	I-II	100°	Impaired vision	Macular changes
	100°							III-IV	110°					
5	OD	750	1	66	10	I	13	90°	II+	34	I	100°	Good vision	Good macula
	90°							III	100°					
6	OD	1140	1	130	3	II	9	100°	III	30	—	110°	Good vision	Good macula
	100°							III	110°					
7	OD	900	3	79	7	I	16	100°	II-III	30	I	100°	Good vision	Good macula
	100°							II-III	100°					
8	OD	1430	30	185	6	I	9	120°	II-III	28	I	120°	Good vision	Good macula
	120°							II-III	120°					
9	OD	880	1	88	8	I	15	120°	II-III	20	—	120°	Good vision	Good macula
	120°							II-III	120°					

OU=both eyes. OD=right eye. OS=left eye. *Angle of main blood vessels emerging from the optic disc.

Among the 533 premature infants studied by us there was an inverse relationship between the birth weight of the infant and the prevalence of acute RLF (see Table 4). It is of note that in the group of premature babies with a birth weight under 1000 g the prevalence of acute RLF was between 61 and 75% (Table 1), and generally the RLF changes were more advanced than in premature babies with RLF with birth weight above 1000 g.

Few statistics have been reported on the results of cryopexy treatment. In the co-operative 5-year study on the natural history of RLF,¹⁴ which involved 5 central intensive neonatal care units, there were 66 infants with acute RLF, of whom 32 were between 1000 and 1200 g birth weight. Of these, 3 became blind due to grades IV and V cicatricial RLF, and 3 had grade III cicatricial RLF, both stages being compatible either with low vision or with legal blindness. Of the 35 premature babies weighing 500–1000 g at birth who were followed up at the Montreal Children's Hospital by Gunn *et al.*¹⁵ 15 (43%) had cicatricial RLF; of these, 6 (20%) children were blind, 10 other children (28%) had high myopia, and 2 more had esotropia.

Since our findings, as well as those of other workers, indicate that the prevalence and severity of RLF are positively related to the degree of retinal prematurity, or in other words to the extent of the zone of avascular hypoxic retinal tissue, it may be assumed that the development of RLF is triggered, as are other ischaemic retinopathies, by a vasoformative substance produced in the ischaemic retina. The larger the stimulus in the area of the available ischaemic retina to produce this substance, the greater would be the vasoproliferation, and hence the greater would be the chance for occurrence of complications leading to cicatricial forms. As in other ischaemic retinopathies, destruction of ischaemic retina is believed to reduce the formation of vasoformative substance and consequently to cause an arrest of the disease.

Our results suggest that such a destruction is easily achieved with cryopexy. In each of the treated eyes there was a rapid resolution or regression of the acute RLF changes. We decided to treat the second eye when it was observed that during the 2–6 weeks of the follow-up period the untreated eye continued to deteriorate, while the previously treated eye showed good regression of the acute RLF.

No complications were encountered which could be attributed to the cryopexy. These findings are unlike those of Kingham,¹² who, in an unrandomised treatment study, reported optic atrophy and severe forms of cicatricial retinopathy after cryoapplication. These different results may be attri-

buted to the differences in the time of treatment, to the surgical technique, and to the location of the cryoapplications. In our mode of treatment we did not attempt to destroy directly the ridge or the neovascular fronds themselves, but applied the cryoprobe only to the avascular peripheral retina, an approach which did not necessitate incising the conjunctiva, pulling muscles, and applying an inevitably stronger pressure on the premature eye. Since we treated the peripheral avascular retina while it was still close to the choroid and not already highly detached, we were able to freeze it properly and by less extensive applications. When the retina is already highly detached, heavy cryoapplication over the sclera and choroid may increase leakage from the choroidal vessels and thus increase the exudative detachment.

In Kingham's report¹² from a series of 101 premature babies of various birth weights, of whom 14 eyes were treated, there was 7% of blindness. We feel that if treatment is performed earlier the rate of blindness should be less, because the acute RLF does not progress to stage IV, a stage in which the chance of successful treatment is, as previously explained, smaller. For the later stages of active, as well as for cicatricial RLF, surgery with an external buckling procedure may be the best solution.¹⁶

In light of the above findings it is encouraging to report that in our preliminary treatment study there was not a single case of blindness among the 55 children with acute RLF, of whom 32 had a birth weight below 1000 g, and none progressed beyond active stage III. These results indicate that cryotherapy used in the method described here is safe and effective in arresting acute RLF and in preventing the progress of the retinopathy towards the severe forms of active and hence cicatricial RLF. The question which remains open is which of the treated children would have had their disease spontaneously regress if left untreated. Since all the children were treated before they reached active stage IV, unlike those in Kingham's series, it is impossible to provide an answer to this question until better criteria for prediction are available.

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