Retinal Artery Tortuosity in ex-Premature Infants

18-year Follow-up on Eyes of Premature Infants

J. DAVID BAUM*

Newborn and Premature Center,† Division of Perinatal Medicine, University of Colorado Medical Center, Denver, Colorado, U.S.A.

Baum, J. D. (1971). *Archives of Disease in Childhood*, 46, 247. **Retinal artery tortuosity in ex-premature infants. 18-year follow-up on eyes of premature infants.** Ophthalmic examinations have been performed on 52 ex-premature infants who had reached their late teens. These patients all weighed 1500 g or less at birth, and were born during a period of transition from liberal to restricted oxygen therapy for premature infants.

Fourteen patients had some degree of retrolental fibrosis. In 4 cases there was complete, bilateral, destructive retrolental fibroplasia (RLF) with microphthalmos; and in 3 cases in which RLF was complete unilaterally, the other eye showed retinal scarring with traction of the disc in 2 patients and extreme tortuosity of the retinal arteries in the third. There were 7 patients who showed bilateral retinal scarring with distortion of the retinal architecture, 35 patients showed tortuosity of the retinal arteries, and 3 patients had normal retinas. It seems that tortuosity of the retinal arteries represents a persistence of the proliferative stage of RLF. In the present study the condition carried no ophthalmic morbidity.

Myopia was associated with retrolental scarring, but not with tortuosity of the retinal arteries. Corneal curvature was normal in these patients, excluding this as the cause of the myopia of RLF.

Oxygen was first recognized as the main factor in the pathogenesis of retrolental fibroplasia (RLF) in 1951 (Campbell, 1951). By 1955 most newborn centres had restricted the amount of oxygen given to newborn infants in their nurseries, with a rapid decline in the incidence of the disease.

Between 1953 and 1955 studies on experimental animals provided an intelligible explanation for the natural history of RLF (Ashton, Ward, and Serpell, 1953; Patz *et al.*, 1953; Ashton, Ward, and Serpell, 1954; Ashton, 1954; Patz, 1954; Gyllensten and Hellström, 1954).

If an immature animal inspired high concentrations of oxygen for long enough, the developing

retinal vessels became severely constricted and the capillaries were obliterated and destroyed. When the animal was transferred to air, the constricted vessels reopened and became dilated and tortuous, while new vessels grew haphazardly both into the ischaemic retina and into the vitreous, exactly as in the early stages of RLF. The degree of neo-vascularization was dependent upon the maturity of the retina, the oxygen concentration, and the duration of exposure (Ashton and Cook, 1954).

Only 25% of infants showing the early proliferative phase of the disease went on to haemorrhage and retinal detachment with fibrous tissue formation behind the lens, and 75% of surviving premature infants developed neither retinal scarring nor complete RLF (Owens, 1953).

Previous studies on surviving infants with lesser grades of retrolental scarring have shown myopia to be a frequent association (Fletcher and Brandon, 1955; Zacharias, Chisholm, and Chapman, 1962). No adequate explanation has been offered for this finding; the possibilities include an excessively

Received 22 December 1970.

* Dr. Baum was in receipt of a Wellcome Trust Research Travel Grant.

† Present address: Department of Child Health, Hammersmith Hospital, Du Cane Road, London W.12.

Supported in part by grants-in-aid from the Maternal and Child Health (HEW) through the Colorado State Department of Public Health and the University of Colorado Medical Center, Maternal and Child Health (HEW) No. H 224.

long axis to the eyeball, excessive corneal curvature, and changes in the refractivity of the ocular media.

In the present study, a group of ex-premature infants have been examined to determine whether there are any persistent ophthalmic changes associated with premature birth, other than retrolental scar formation. Measurements have also been made for refractive error and corneal curvature of this group of patients in an attempt to clarify the association between myopia and RLF.

Methods and Materials

Of 160 surviving premature infants with birthweights of 1500 g or less, admitted between 1950 and 1953 to the University of Colorado Medical Center, 52 were available for follow-up studies. The years 1950-53 were chosen to represent a period of transition with regard to oxygen therapy. Up until 1951 oxygen was used liberally and in high concentrations. Subsequently in this centre its use was severely restricted, more than 40% being used only in infants with respiratory failure and cyanosis.

Each of the 52 young adults seen was studied ophthalmoscopically using a direct ophthalmoscope after dilatation of the pupil with 0.5% cyclopentolate.

Retinal photographs were taken, and refractive errors measured. In a small group of patients the curvature of the cornea was measured by keratometry. In this technique an illuminated object is projected from a fixed distance on to the cornea which acts as a convex mirror. From the size of the reflected image the keratometer computes the curvature of the cornea, which is read off directly in diopters.

From the hospital charts of these patients, data were collected on birthweight, gestational age (where mother's dates were available and certain), and the amount of oxygen received. This amount was translated into an oxygen score from 0-10 according to the concentration and duration of exposure (Table I).

The retinal findings were recorded at the time of the examination. Grades of tortuosity of the retinal

arteries were later confirmed by reviewing the retinal photographs and were expressed on a scale from 0-3 for each eye, giving a maximum score of 6 per patient.

Results

Fifty-two patients were examined. The range of birthweights and gestational ages is shown in Table II. The retinal findings are summarized in Table III.

TABLE II

Birthweight and Gestational Age Range of Sample

	No. of Patients Seen	Mean	SD	Range
Birthweight (g)	52	1168	187	709-1500
Gestational age (wk)	44	30	2.7	26-39

NOTE: In 12 cases, gestational age was uncertain.
In 7 cases, the infants were of small weight for their gestational age (SGA).

TABLE III

Retinal Findings

Retinal Findings	No. of Patients
Bilateral complete RLF	4
Unilateral complete RLF	3
Bilateral retinal scarring	7
Arterial tortuosity* = 1	2
2	4
3	1
4	7
5	0
6	21
Normal	3
Total	52

* Arterial tortuosity was expressed on a scale from 0-3 for each eye, giving a maximum score of 6 for each patient.

TABLE I
Oxygen Score

O ₂ Concentration Air	Duration	Score
<40%	<24 hr	1
	24-1 wk	2
	1-2 wk	3
	2-4 wk	4
	>4 wk	5
>40%	<12 hr	1
	12-24 hr	2
	24-72 hr	3
	72 hr-1 wk	4
	>1 wk	5
	Total	30

Fourteen patients had some degree of retrolental fibrosis. In 4 cases there was complete bilateral destructive RLF with microphthalmos; and in 3 cases in which RLF was complete unilaterally, the other eye showed retinal scarring with traction of the disc in 2 patients and extreme tortuosity of the retinal arteries in the third. There were 7 patients who showed bilateral retinal scarring with distortion of the retinal architecture, temporal traction of the disc, and patchy retinal pigmentation (Fig. 1). Thirty-five patients showed abnormal tortuosity of the retinal arteries. The arteries were distinctly more tortuous than the veins; the degree of tortuosity was similar in both eyes. In those cases with slight tortuosity the vessels affected were

FIG. 1.—Retrolental scar formation with temporal traction of the disc and patchy retinal pigmentation (left eye).

FIG. 2.—Tortuosity score = 1 predominantly affecting the inferior temporal artery (left eye).

the superior and inferior temporal arteries. Examples of tortuosity scores 1, 2, and 3 are shown in Fig. 2, 3, and 4. Where there was frank retinal scarring, the vessels appeared unusually straight rather than tortuous (Fig. 1). Three patients had normal retinas.

Forty-three patients were refracted. Where both eyes could be tested, the refractive error was similar. The distribution of refractive errors is shown in Table IV. The patients with retinal scarring showed significant myopia, with refractive

errors ranging from -3 to -26 diopters. Patients with tortuosity of the retinal arteries showed no definite pattern of refraction, but had refractive errors ranging from $+5$ to -6 diopters: 16 of these patients (48.5%) had no refractive error (emmetropic).

Corneal curvature was measured in 10 patients who were myopic and showed extreme arterial tortuosity or retinal scarring (Table V). These measurements of corneal curvature were within the normal limits for adults.

FIG. 3.—Tortuosity score = 2, affecting the temporal and other retinal arteries (left eye).

FIG. 4.—Tortuosity score = 3, showing hairpin bends in many of the retinal arteries (left eye).

TABLE IV
Refractive Errors in 43 Patients with Either Retinal Scarring or Tortuosity of Retinal Arteries

	Refractive Error in Diopters										
	+5	+1	0	-1	-2	-3	-3	-5	-6	-15	-26
Patients with retinal scarring						1	4	1	2	1	1
Patients with arterial tortuosity	2	1	16	4	4	3	1	1	1		

TABLE V
Corneal Curvature

	No. of Cases	Refractive Error Diopters		Corneal Curvature Diopters		Normal Adult Corneal Curvature Diopters	
		Mean	Range	Mean	Range	Mean	Range to cover ± 2 SD
Tortuosity 6 +	5	-4.4	-2.75 to -6.0	44.9	41.75 to 47.25	44	
Retinal scarring	5	-9.6	-4.5 to -26	44.3	41.25 to 47.5		41.6 to 47

(Normal data from 2000 adult patients as measured by the National Eye Research Foundation.) A. Prechtel, 1970, personal communication.

TABLE VI
Correlation Coefficients

	Birthweight	Gestational Age	SGA/AGA	Oxygen Score	Refractive Error
Complete RLF	-0.381†	-0.118	-0.128	0.276*	—
Retinal scarring	0.025	-0.040	0.035	-0.212	-0.382‡
Tortuosity	0.026	-0.276*	0.343*	-0.012	0.111

* Denotes significance at 5% level.

† Denotes significance at 1% level.

‡ All patients with retinal scarring were myopic. Since myopia is measured in negative diopters the correlation coefficient carries a negative sign.

Tests of correlation were made between complete RLF, retinal scarring, tortuosity score and birthweight, gestational age, oxygen score, and refractive error (Table VI). Complete RLF was significantly associated with low birthweight and high oxygen score; retinal scarring correlated with myopia; and arterial tortuosity was associated with low gestational age but was significantly less evident in those cases known to have been small in weight for their gestational age (SGA).

Discussion

In the early clinical descriptions of RLF, gross dilatation and tortuosity of both the retinal arteries and veins was noted as a common early pointer to the disease (Fig. 5) (Owens and Owens, 1949). Among infants with these changes, only a minority went on to retinal detachment and permanent damage from scarring or complete RLF (Owens, 1953).

Hix (1953) noted an association between the degree of tortuosity of the retinal arteries in the proliferative phase of the disease, and the likelihood of developing destructive RLF. He also observed that tortuosity was most obvious in the temporal arteries and that it persisted up to 3 months of age. Tassman and Annesley (1966) mentioned the presence of persistent tortuosity of the retinal vessels in some cases of non-destructive RLF which went on to retinal tears and detachment in late childhood or early adult life.

In the present group of patients, 4 had bilateral complete RLF; 3 had unilateral complete RLF in association with scarring or vascular tortuosity in the other eye; 7 had bilateral retinal scarring; 35 had some degree of arterial tortuosity; 3 had normal eyes.

It is recognized that there is great biological variation in the susceptibility of premature infants to RLF. Moreover, a retrospective assessment of

FIG. 5.—A drawing of the proliferative phase of RLF taken from a paper by Owens and Owens (1949) (reproduced by permission of the authors and publishers), showing tortuosity with hairpin bends in the retinal arteries. This is very similar in appearance to the photograph of 3+ tortuosity shown in Fig. 4.

oxygen dosage takes no account of the degrees of respiratory failure present and the likely levels of arterial oxygenation reached. These factors may explain the findings in the present study: while complete RLF is present in the infants of smallest birthweight, and those with the highest oxygen scores, retrolental scarring showed no such association. Tortuosity of the retinal arteries was associated with low gestational age and was significantly less obvious in the 7 patients who were small for gestational age at birth. It should be noted that all the patients were from a population of premature infants of birthweights of 1500 g or less.

The finding of myopia in partial RLF has been noted previously (Fletcher and Brandon, 1955; Zacharias *et al.*, 1962). In this study, there was a significant association between RLF and myopia with degrees of myopia ranging from -3 to -26 diopters. The severity of these errors of refraction may be judged by the fact that a patient with only -2 diopters of myopia would need to wear glasses for all normal daily activities. Those patients exhibiting arterial tortuosity showed no definite pattern of refractive error. No satisfactory explanation has been offered for the myopia of RLF. In the present study the curvature of the cornea in 10 patients was within normal limits (Prechtel, 1970, personal communication), even in association with extreme myopia.

This includes excessive corneal curvature as an explanation for this phenomenon.

Tortuosity of the retinal vessels is a common finding in the early stages of RLF (Fig. 5) (Owens and Owens, 1949). In the majority of published cases, patients with lesser degrees of retinal scarring had lesions located at the temporal periphery (Reese and Stepanik, 1954). It is known that the temporal periphery of the retina is the latest to develop a mature vasculature (Cogan, 1963).

Tortuosity of the retinal arteries has been described as a very rare congenital anomaly (Duke-Elder, 1963). However, from the prevalence of this condition in the group of ex-premature infants studied and from its predominance in the temporal retinal arteries, it seems likely that this represents a *forme fruste* of RLF. Moreover, the SGA infants had significantly lesser degrees of tortuosity; presumably the retinal vessels would be more mature at birth in this group of patients compared with AGA infants of similar birthweight. It appears that in those cases of proliferative RLF which do not progress to retinal scarring, the early changes in the retinal arteries persist; the retinal veins return to normal. In the present study the condition carried no morbidity.

I thank Professor Philip P. Ellis, Department of Ophthalmology, for allowing me to use the facilities in the Eye Clinic; Dr. Barbara Arnold, and other Ophthalmic House Staff for their assistance in refracting these patients, and Donald Searls, Ph.D., Westat Research Associates, for his help in the statistical analysis of data.

REFERENCES

- Ashton, N. (1954). Pathological basis of retrolental fibroplasia. *British Journal of Ophthalmology*, **38**, 385.
- Ashton, N., and Cook, C. (1954). Direct observation of the effect of oxygen on developing vessels. *British Journal of Ophthalmology*, **38**, 433.
- Ashton, N., Ward, B., and Serpell, G. (1953). Role of oxygen in the genesis of retrolental fibroplasia. *British Journal of Ophthalmology*, **37**, 513.
- Ashton, N., Ward, B., and Serpell, G. (1954). Effect of oxygen on developing retinal vessels with particular reference to the problem of retrolental fibroplasia. *British Journal of Ophthalmology*, **38**, 397.
- Campbell, K. (1951). Intensive oxygen therapy as a possible cause of retrolental fibroplasia. *Medical Journal of Australia*, **2**, 48.
- Cogan, D. G. (1963). Development and senescence of the human retinal vasculature. *Transactions of the Ophthalmological Society of the United Kingdom*, **83**, 465.
- Duke-Elder, S. (1963). Tortuosity of the retinal vessels. In *System of Ophthalmology*. Vol. III, part 2, *Congenital Deformities*, p. 784. Kimpton, London. C. V. Mosby, St. Louis.
- Fletcher, M. C., and Brandon, S. (1955). Myopia of prematurity. *American Journal of Ophthalmology*, **40**, 474.
- Gyllenstein, L. J., and Hellström, B. E. (1954). Experimental approach to the pathogenesis of retrolental fibroplasia. *Acta Paediatrica*, Suppl. 100, p. 131.
- Hix, I. E., Jr. (1953). A review of retrolental fibroplasia, with an analysis of the fundoscopic appearance as an aid to prognosis. M.D. Thesis, University of Colorado.

- Owens, W. C. (1953). Spontaneous regression in retrolental fibroplasia. *Transactions of the American Ophthalmological Society*, **51**, 555.
- Owens, W. C., and Owens, E. U. (1949). Retrolental fibroplasia in premature infants. *American Journal of Ophthalmology*, **32**, 1.
- Patz, A. (1954). Oxygen studies in retrolental fibroplasia. IV. Clinical and experimental observations. *American Journal of Ophthalmology*, **38**, 291.
- Patz, A., Eastham, A., Higginbotham, D. H., and Kleh, T. (1953). Oxygen studies in retrolental fibroplasia. *American Journal of Ophthalmology*, **36**, 1511.
- Reese, A. B., and Stepanik, J. (1954). Cicatricial stage of retrolental fibroplasia. *American Journal of Ophthalmology*, **38**, 308.
- Tassman, W., and Annesley, W., Jr. (1966). Retinal detachment in the retinopathy of prematurity. *Archives of Ophthalmology*, **75**, 608.
- Zacharias, L., Chisholm, J. F., Jr., and Chapman, R. B. (1962). Visual and ocular damage in retrolental fibroplasia. *American Journal of Ophthalmology*, **53**, 337.

Correspondence to Dr. J. D. Baum, Department of Child Health, Hammersmith Hospital, Du Cane Road, London W.12.