Graefes Arch Clin Exp Ophthalmol (2013) 251:2093–2097
DOI 10.1007/s00417-013-2321-8

RETINAL DISORDERS

Early retinopathy of prematurity findings identified with fluorescein angiography

L. Consuelo Zepeda-Romero · Aldo A. Oregon-Miranda · Dalia S. Lizarraga-Barrón · Oscar Gutiérrez-Camarena · Alonso Meza-Anguiano · José Alfonso Gutiérrez-Padilla

Received: 27 September 2012 / Revised: 27 February 2013 / Accepted: 12 March 2013 / Published online: 2 April 2013

Abstract
Background Fluorescein angiography has been fundamental for the understanding and description of vascular disorders affecting the retina and choroid. The aim of this report is to assess the early anatomic retinal changes visible with angiography, and their relation with the clinical findings of retinopathy of prematurity.

Methods Ten babies were included in the study, the initial examination being at 2 weeks after birth. Two cycles of tropicamide 0.8 % and phenylephrine 5 % eye drops were instilled into both eyes 30 min before examination. A RetCam II was used to obtain digital retinal images, after instilling topical anesthesia (tetracain 0.5 %) and using a contact gel. Fluorescein angiography was undertaken following administration of an intravenous bolus of 0.1 ml/kg saline fluorescein 10 % followed by a 3.0-ml isotonic saline flush, with the assistance of the neonatologist; the right and left eyes were imaged.
Results We observed that some of the vascular abnormalities described for threshold disease by Lepore were already present at the second week of life, preceding the diagnosis of threshold disease by 3–4 weeks in two cases. The main findings in our cases were arterio-venous shunts, surrounded by areas of capillary non-perfusion, rosary-bead-like hyperfluorescence, tortuosity and leakage from distal arterioles, none of which were detectable in the digital fundus pictures.
Conclusions Early ROP screening at the NICU that includes FA is a safe procedure, and gives the examiner details of vascular changes that are not detectable by indirect ophthalmoscopy, which could predict the progression to threshold disease, and provide an alert about the need of therapeutic interventions.

Keywords ROP RetCam · Fluorescein angiography · ROP screening · Tropicamide

Presentation at a conference This work was presented as a poster at the ARVO 2010 meeting.

The authors have full control of all primary data, and they agree to allow Graefe's Archive for Clinical and Experimental Ophthalmology to review their data if requested.

L. C. Zepeda-Romero
Clinic of Retinopathy of Prematurity and Blindness prevention, Hospital Civil de Guadalajara, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Guadalajara, Mexico

A. A. Oregon-Miranda · D. S. Lizarraga-Barrón
Hospital Civil de Guadalajara,
Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Guadalajara, Mexico

O. Gutiérrez-Camarena · J. A. Gutiérrez-Padilla
Unidad de Cuidados Intensivos Neonatales UCINEX, Hospital Civil de Guadalajara, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Guadalajara, Mexico

A. Meza-Anguiano
Hospital Civil de Guadalajara, Universidad Guadalajara LAMAR, Guadalajara, Mexico

L. C. Zepeda-Romero (✉)
Clinic of Retinopathy of Prematurity and Blindness prevention, Hospital Civil de Guadalajara Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara,
Calle Boulevard Puerta de Hierro 5150,
Zapopan, Jalisco, Mexico 45116
e-mail: drconsuelo@yahoo.com

Introduction

Fluorescein angiography (FA) has been fundamental to the understanding and description of vascular disorders

affecting the retina and choroid (1), and previous reports suggest that FA can also be useful in delineating the vasculature of premature infants when the ocular media are hazy (2). Fluorescein angiography has also been useful in identifying features of the choroidal and retinal circulation in established ROP which are not visible clinically, and improves our understanding of the pathogenesis and natural history of ROP (2–5). However, in the majority of studies undertaken to date, FA has been performed either at the time of treatment with laser or anti-VEGF preparations for type 1 pre-threshold ROP, or at the time of vitreo-retinal surgery for the more advanced stages of the disease. However, it is known that risk factors for ROP exert their effects early in the neonatal period. We report vascular findings identified by FA while screening two preterm babies in the second week after birth. Both subsequently went on to develop pre-threshold disease.

Material and methods

Ten babies were included in the study. After obtaining informed consent from the parents, ophthalmic examinations were performed in the neonatal unit, with the initial examination being at 2 weeks after birth. Two cycles of tropicamide 0.8 % and phenylephrine 5 % eye drops were instilled into both eyes 30 min before examination. A RetCam II (Massie Research Laboratories, Inc., Pleasanton, CA, USA) was used to obtain digital retinal images, after instilling topical anesthesia (tetracain 0.5 %), using a contact gel, and taking care not to put pressure on the globe. Fluorescein angiography was undertaken following administration of an intravenous bolus of 0.1 ml/kg saline fluorescein 10 % (Sophia Labs. Jalisco, Mexico) followed by a 3.0-ml isotonic saline flush, with the assistance of the neonatologist, using the RetCam and its blue excitation light source and yellow-green filter; the right and left eyes were imaged.

Results

These were very complex babies in which no adverse events were reported during the exam. The mean birth weight of the eight infants without ROP type 1 was 1,311 g (range, 1,050–1,560 g) and the mean gestational age was 29.5 weeks (range, 26–31.2 weeks). In four eyes of two babies, ROP progressed to type 1 ETROP disease, and peripheral retinal laser was applied. In another neonate, ROP developed in zone 2, which resolved spontaneously. The FA findings and demographic characteristics of the ten babies are summarized in Table 1.

Table 1 Demographic characteristics and FA findings

Name	G	GA	BW	Findings at 2 weeks	Final diagnostic
Case 1	M	30.5 sdg	1,280 g	Irregular choroidal pattern, arterioles with rosary-bead-like tortuosity, arterio-venous shunts, capillary lost and multiple non-perfused areas, one surrounding foveal avascular zone.	ROP TYPE 1
Case 2	M	32 sdg	1,119 g	Irregular choroidal pattern, arterio-venus shunts, surrounding non-perfused area, focal capillary dilatation and tortuosity, with leakage and capillary lost, rosary-bead-like hyperfluorescence.	ROP TYPE 1
Control 1	M	31.2 sdg	1,270 g	Regular capillary distribution with dichotomous pattern towards the peripheral, distal loops with vascular tufts towards periphery, macular area with foveal avascular zone.	NO ROP
Control 2	M	30 sdg	1,405 g	Fluorescein in choroidal circulation but not in retinal capillaries.	NO ROP
Control 3	F	30 sdg	1,450 g	Regular capillary distribution with dichotomous pattern towards the periphery, capillary distal tufts and macular area with foveal avascular zone.	NO ROP
Control 4	F	30 sdg	1,245 g	Fluorescein in choroidal circulation but not in retinal capillaries.	NO ROP
Control 5	F	26 sdg	1,050 g	Capillaries with discrete tortuosity, distal A-V shunts with leakage that compromise foveal area, capillary ends and loop with presence of vascular tufts directed towards the periphery.	ROP 2, regression
Control 6	F	28 sdg	1,175 g	No fluorescein evidence in retinal circulation, evidence of fluorescein at the skin.	NO ROP
Control 7	M	29.3 sdg	1,560 g	Regular capillary distribution with dichotomous pattern towards the periphery, macular area with foveal avascular zone and distal tufts at capillary end.	NO ROP
Control 8	F	30 sdg	1,352 g	Regular capillary distribution with dichotomous pattern towards the periphery, macular area with foveal avascular zone.	NO ROP

BW birth weight, *GA* gestional age, *G* gender

Case 1: Boy born at a community center: gestational age, 30.5 weeks and birth weight, 1,080 g. He was the first child of a 19-year-old woman and he was born by vaginal delivery. The mother had a history of recurrent urinary infections during pregnancy. At birth, neonatal respiratory distress was diagnosed, and the baby was referred to the NICU where he was ventilated for 3 days. After this, he was on CPAP for 4 days, and then nasal positive pressure oxygen was established. His arterial oxygen saturation levels averaged 99 %. Erythropoietin was administrated every 72 h for 1 month, with an average dose of 360 IU. By week 36 of corrected gestational age, the diagnosis of ROP stage 3 in zone 2 was made, and diode laser photo ablation was applied to both eyes.

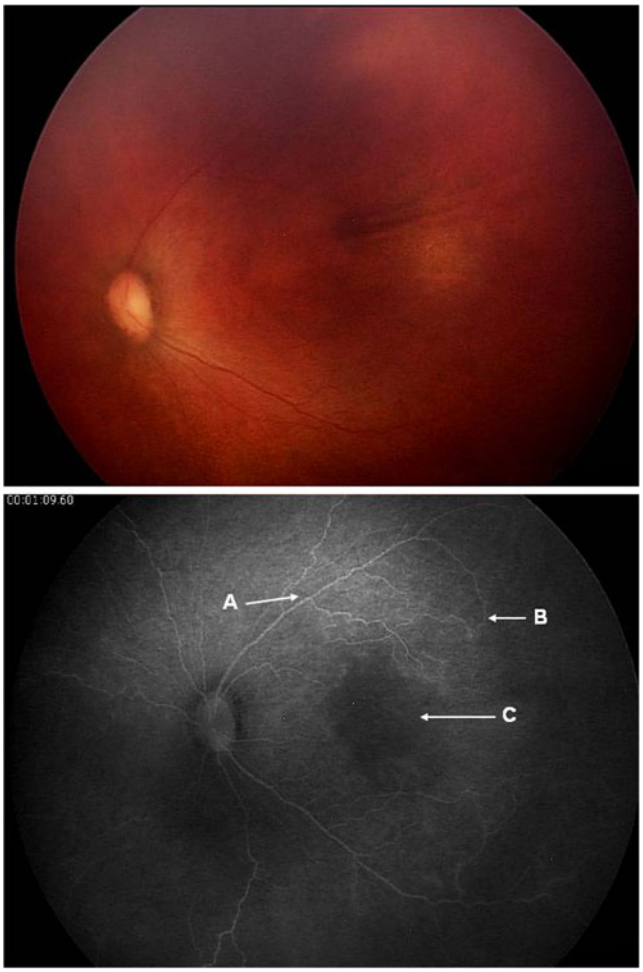

Fig. 1 Case 1. Left eye fundus color picture showing vascular development up to zone 2. Fluorescein angiography, at 1:09 min showing an irregular choroidal pattern, arterioles with rosary-bead-like tortuosity (**a**), arterio-venous shunts (**b**), capillary lost and multiple non-perfussed areas, one surrounding foveal avascular zone (**c**)

Case 2: Boy born at the Regional Hospital: gestational age, 32 weeks and birth weight, 1,119 g. He was the third child of a 24-year-old woman who had not received any prenatal care. On day 3, bacteremia was diagnosed and he was transferred to a neonatal therapy unit, where he had oxygen therapy using nasal positive oxygen pressure for 14 days with average blood oxygen saturation of 98 %, followed by environmental oxygen supplement within the incubator. Erythropoietin was administered with a dose of 320 IU. ROP stage 3 in zone 2 with plus disease was diagnosed on week 5, with vitreo-retinal neovascularization (popcorn), and diode laser photo ablation was applied in both eyes.

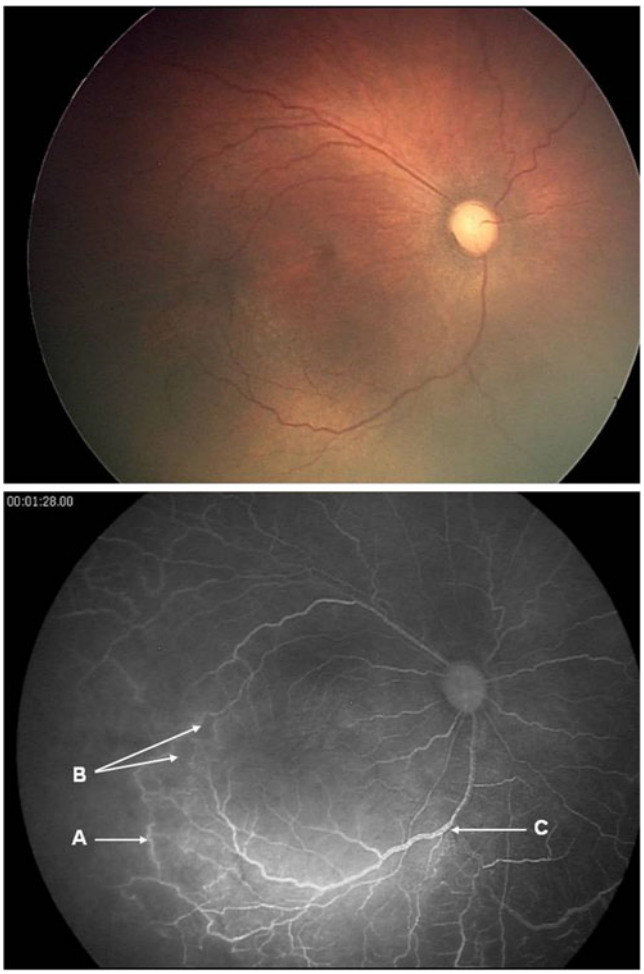

Fig. 2 Case 2. Right eye fundus color picture, showing vessels developed at posterior zone 2. Fluorescein angiography, at 88 s showing an irregular choroidal pattern, arterio-venous shunt (**a**), surrounding non-perfussed area with capillary lost (**b**), focal capillary dilatation and tortuosity, with leakage and capillary tufts, rosary-bead-like hyperfluorescence (**c**), distal tortuosity and leakage from the distal arterioles

In these cases, findings visible with FA were (Figs. 1 and 2) arterio-venous shunts, surrounding areas of capillary lost, rosary-bead-like hyper-fluorescence, arteriolar tortuosity and leakage from distal arterioles, and areas of retinal ischemia, none of which were detectable in the digital fundus pictures.

Some of the findings were visible in the FA of the case that developed stage 2 ROP, such as capillaries with discrete tortuosity, distal A-V shunts with leakage that compromise foveal area, without identifying ischemic areas (Fig. 3). None of these findings are present in the control eyes, i.e., those eyes that did not develop ROP. They did not show areas of ischemia, capillary loss, or arterio-venous shunts. (Fig. 4)

Discussion

Early ROP screening at the NICU that includes FA is a safe procedure, and gives the examiner details about retinal perfusion and vascular changes that are not detectable by indirect ophthalmoscopy. Some of the findings identifiable at the second week after birth were already described for threshold disease by Lepore (5), preceding the diagnosis of threshold disease by 3–4 weeks.

As proposed by Cantolino et al. (6) these findings could predict the progression to threshold disease, and provide an alert about the need of therapeutic interventions. The presence of ischemic retinal areas might be the distinctive sign for the cases that develop type 1 ROP.

Further clinical trials are required to assess this, and the absence of fluorescein in the retinal circulation of some cases. The similarity of these findings with those described for oxygen-induced retinopathy in animal models (7) should provide an alert about the urgent need of controlling risk factors such as the levels of oxygen in this population.

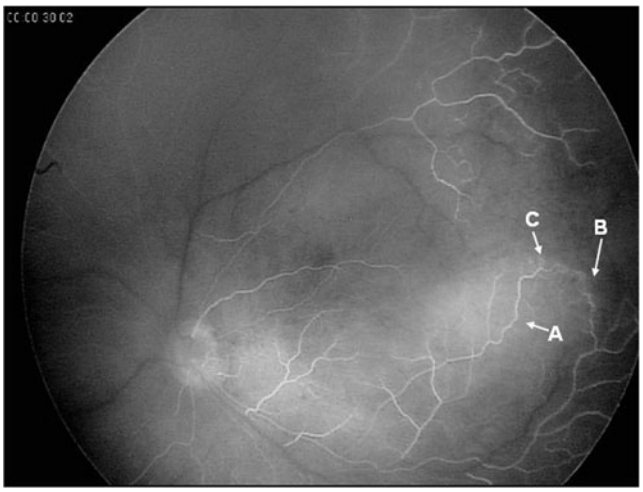

Fig. 3 Control 5. Left eye fluorescein angiography picture, at 30 s showing an early arterio-venous phase, vascular development up to zone 2, capillaries with discrete tortuosity (**a**). Distal A-V shunts (**b**) with leakage that compromise foveal area. Capillary ends and loop with presence of vascular tufts directed towards the periphery (**c**)

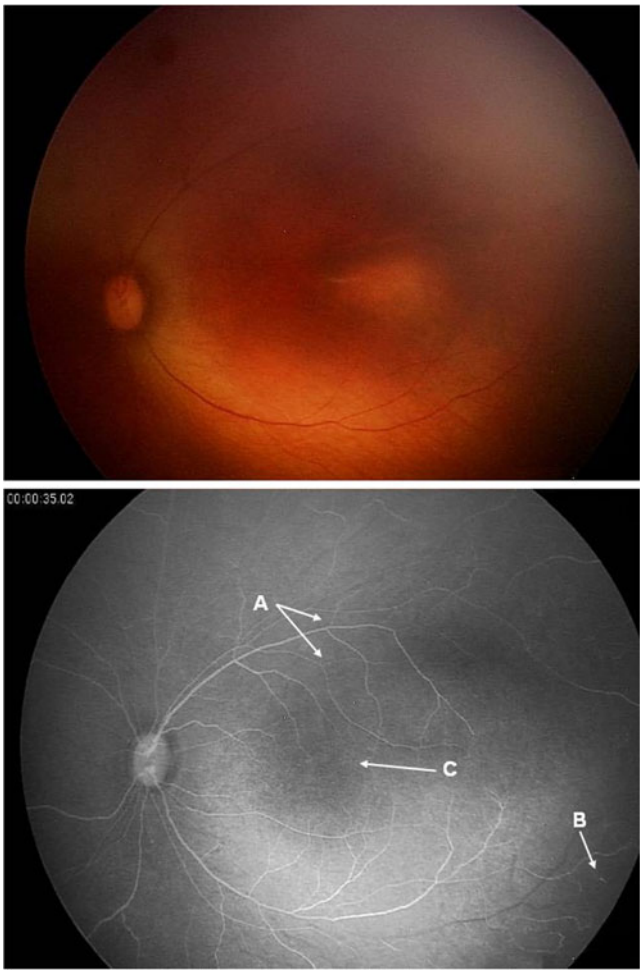

Fig. 4 Control 1. Left eye fundus color picture, showing vascular development up to zone 2. Fluorescein angiography, at 35 s showing regular capillary distribution with dichotomous pattern towards the peripheral (**a**), distal loops with vascular tufts towards periphery (**b**), macular area with foveal avascular zone (**c**)

Conflict of interest The authors declare no funding, no competing interest in the preparation of this manuscript. The authors don't have a financial interest in the research.

References

1. Novotny HR, Alvis DL (1961) A method of photographing fluorescence in circulating blood in the human retina. Circulation 24:82–86
2. Yokoi T, Hiraoka M, Miyamoto M, Yokoi T, Kobayashi Y, Nishina S, Azuma N (2009) Vascular abnormalities in aggressive posterior retinopathy of prematurity detected by fluorescein angiography. Ophthalmology 116(7):1377–1382

3. Wagner RS (2006) Fundus fluorescein angiography in retinopathy of prematurity. J Pediatr Ophthalmol Strabismus 43(2):78
4. Ng EY, Lanigan B, O'Keefe M (2006) Fundus fluorescein angiography in the screening for and management for retinopathy of prematurity. J Pediatr Ophthalmol Strabismus 43(2):85–90
5. Lepore D, Molle F, Pagliara M, Baldascino A, Angora C, Sammartino M, Quinn G (2011) Atlas of fluorescein angiographic findings in eyes undergoing laser for retinopathy of prematurity. Ophthalmology 118:168–175
6. Cantolino SJ, O'Grady G, Herrera J, Israel C, Justice J, Flynn J (1971) Ophthalmoscopic monitoring of oxygen therapy in premature infants. Am J Ophthalmol 72(2):322–331
7. Smith LE, Wesolowski E, McLellan A, Kostyk SK, D'Amato R, Sullivan R, D'Amore PA (1994) Oxygen-induced retinopathy in the mouse. Invest Ophthalmol Vis Sci 35(1):101–111