

Congenital cataract associated with persistent fetal vasculature – findings from IoLunder2

Authors:

Ameenat Lola Solebo^{1,2,3,4}, Isabelle Russell-Eggitt^{2,4}, Phillippa Cumberland^{1,4}, Jugnoo S Rahi^{1,2,3,4}, on behalf of the British Isles Congenital Cataract Interest Group

1. Lifecourse Epidemiology and Biostatistics Section, Population, Policy and Practice Programme, Institute of Child Health University College London, 30 Guilford Street, London, WC1N 1EH, UK
2. Great Ormond Street Hospital / Institute of Child Health NIHR Biomedical Research Centre, London
3. Moorfields Eye Hospital and Institute of Ophthalmology NIHR Biomedical Research Centre, London
4. Ulverscroft Vision Research Group, London

Corresponding Author (and address for reprints)

Professor J S Rahi

Lifecourse Epidemiology and Biostatistics Section, Population, Policy and Practice Programme

University College London Institute of Child Health
30 Guilford Street, London, WC1N 1EH, UK

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Abstract (250)

Aim: to describe the frequency, characteristics and treatment outcome of persistent fetal vasculature (PFV) in children undergoing surgery for congenital and infantile cataract in the first two years of life

Methods: observational population based cohort study with case identification through active surveillance and standardised data collection via a national clinical network, the British Isles Congenital Cataract Interest Group (BCCIG)

Results: The IoLunder2 cohort comprises 246 children undergoing surgery for bilateral and unilateral congenital and infantile cataract in the first two years of life. 58/246 (24%) children had persistent fetal vasculature (%): overall, 46/95 (46%) with unilateral cataract, and 12/141 (8%) with bilateral disease. Anterior segment vascular remnants were more common in bilateral than unilateral disease (75% versus 11%, $p=0.01$). At one year after surgery, 20% of children with bilateral PFV and 24% with unilateral had achieved normal vision for age within the operated eye. The prevalence of post operative glaucoma was 9% (of children with bilateral disease) and 4% (unilateral).

Conclusions: persistent fetal vasculature is significantly more common than previously reported, and outcomes are comparable to that for congenital and infantile cataract overall.

Persistent fetal vasculature, or PFV, comprises a spectrum of clinical features caused by failure of the normal process of regression or apoptosis of the fetal intraocular vasculature which usually occurs during the second trimester. PFV was previously termed persistent hyperplastic primary vitreous (PHPV), due to the characteristic feature of a plaque of remnant tissue sitting on the posterior face of a cataractous lens, attached to a persistent stalk of hyaloid vasculature. However, any part of the fetal vasculature can persist, resulting in iris, pupillary, or optic nerve vascular remnants.(1) Congenital pupillary fibrovascular membranes, rather than being a separate entity, are histopathologically similar to the retrolenticular manifestations of PFV.(2)

Cataract is a frequent secondary event in PFV, due to invasion of the vascular remnants, lenticular swelling, intralenticular haemorrhage, or calcification.(1,3) PFV features have been found in a fifth of cases of unilateral congenital or infantile cataract, but are much less commonly noted in bilateral cataract.(4) Cataract surgery in children with PFV is associated with a higher incidence of adverse events and worse outcome.(5;6) In addition, bilateral cases of PFV may be associated with systemic abnormalities which impact on a child's global development.(1;7)

The British Isles study of primary intraocular lens implantation in children under 2 with congenital or infantile cataract (IoLunder2) is a prospective observational cohort study, undertaken through the British Isles Congenital Cataract Interest Group (BCCIG) a collaborative clinical research network of ophthalmologists involved in the management of children with congenital and infantile cataract. IoLunder2, which comprises a nationally representative group of children who have undergone cataract extraction with or without intraocular lens implantation in the United

Kingdom and Ireland, aims to describe treatment outcomes and determine the predictors of outcome. We report here on the morphology of persistent fetal vasculature and outcomes following surgery within this cohort.

Methods

Children eligible for inclusion into the IoLunder2 study were those resident in the British Isles undergoing primary surgery for congenital or infantile cataract in the first two years of life. Active surveillance was undertaken over a two year study period (January 2009 to December 2010) through a national clinical network, the British Isles Congenital Cataract Interest Group (BCCIG). Following parental consent, standardised data collection using a structured proforma was undertaken through the network. The IoLunder2 study methodology has been reported in detail previously.(8)

A standardised classification of the presence and morphology of PFV was developed for the study. PFV was classified within one of these three mutually exclusive categories using an anatomically derived taxonomy (see e-supplement):

- 1. Isolated posterior capsular plaque / persistent posterior tunica vasculosa*
- 2. Anterior PFV only (persistent iridohyaloid / pupillary membrane / anterior tunica vasculosa)*
- 3. Complex PFV (posterior plaque plus other manifestation)*

Within the complex PFV category, the presence of other signs (anterior PFV, persistent hyaloid artery, centrally dragged ciliary processes, optic nerve head

hypoplasia / dysplasia, macular abnormalities, retinal detachment) were dichotomised as present or absent.

Statistical analyses were performed using STATA SE 10/11 (Stata Corp, Chicago Illinois). Children with unilateral cataract were analysed separately from those with bilateral disease. Findings of descriptive analysis are presented as proportions for binary or categorical data, with 95% confidence intervals where appropriate.

Ethics and research governance approval was granted by the relevant UK / Ireland bodies, and the research adhered to the tenets of the Declaration of Helsinki.

Results:

254 (83%) of eligible children were recruited into IOLunder2. Complete pre and post-operative data are available for 246, and post-operative outcomes at one year following surgery were available for 221. Persistent fetal vasculature was present in 58 of the 246 children (23.6%, table 1): 46 of the 99 children with unilateral cataract (46.5%, 95% confidence interval CI 36 to 56%), and a significantly lower proportion of children with bilateral cataract (12/147 children, 8.2%, 95% CI 0 to 24%).

Compared to other children with unilateral congenital and infantile cataract, those with persistent fetal vasculature presented to clinicians at a similar age. All children with unilateral congenital cataract associated with PFV had negative family histories for congenital cataract. Compared to other children with bilateral cataract, diagnosis of PFV cataract occurred at a later age, children were less likely to have a family history of cataract, and more likely to be affected by a systemic disorder or anomaly, although these differences did not reach statistical significance (table 2).

Table 1. Classification of persistent fetal vasculature in bilateral and unilateral congenital and infantile cataract

	Bilateral	Unilateral	Total
Number of children	147	99	246
Number of children with PFV	12	46	58
% of children	8.2%	46.5%	23.6%
Isolated retroental PFV	2	19	21
% of children with PFV	17%	43%	37%
Anterior PFV	4	3	7
%	33%	7%	13%
Complex PFV	6	23	29
%	50%	50%	50%

Manifestations of PFV in unilateral and bilateral cataract

The most common finding in PFV associated unilateral cataract was persistent posterior tunica vasculosa lentis (PTVL), manifesting as either a posterior plaque or membrane (41 children, 92%) (figure 1a). However, for half of all children with a persistent hyaloid artery (9/18), there was no other retrolental vascular manifestation (figure 1a). Bilateral PFV was more likely to have present as something other than the classic retrolental plaque: in comparison to children with unilateral PFV, a significantly higher proportion of children with bilateral PFV associated cataract had iris, pupil or anterior capsular vascular remnants (75% versus 11%, χ^2 test for difference between proportions or DIP $p=0.01$, 95% CI DIP 21% - 71%). Bilateral PFV also showed evidence of within child phenotypic variation: in 2 of the 7 cases of bilateral PFV, children had asymmetric manifestations of persistence in both eyes. In comparison to congenital and infantile cataract with no evidence of PFV, bilateral and unilateral cataract eyes with evidence of persistent vasculature were no more likely to be microphthalmic. No child with bilateral disease had stretched ciliary processes, whilst 8 children (18%, 95% CI 7-29%) with unilateral PFV exhibited ciliary process traction (figure 1b).

Table 2. Clinical characteristics and outcome for children with persistent fetal vasculature related cataract versus cataract without PFV

		PFV associated unilateral cataract n=46	Unilateral cataract without PFV n=53	PFV associated bilateral cataract n=12	Bilateral cataract without PFV n=129
Median age at diagnosis (range in days)		13 days (1 – 671)	16 days (0 - 486)	49 days (2 – 275)	6 days (0-586)
Positive family history of cataract (95% CI)		0% (0-1)	9%* (1-16)	25% (1-50)	45% (36-54)
Cataract morphology	Posterior lenticular opacity, % (95% CI)	61% (47-75)	19%* (8-30)	42% (14-70)	10% (5-15)
	Anterior lenticular opacity, %	1%	9%	8%	3%
	Other, %	38%	72%	50%	87%
Prevalence of non-ophthalmic systemic disorder (95% CI)		4% (0-10)	7% (1-14)	58% (31-86)	20% (13-27)
Median axial length in mm (range)		18.1 (15-22.9)	18.5 (15.3 – 23.9)	18.0 (15.4 – 24.1)	17.5 (13.3 - 23.5)
Median horizontal corneal diameter in mm (range)		10.25 (8-12)	10.5 (9-12.5)	9.5 (7-12)	10 (7.25 – 12)
Median age at surgery (range)		9 weeks (4- 100)	9 weeks (2 – 95)	19 weeks (4-64)	10 weeks (2 – 101)
Proportion undergoing IoL implantation (95% CI)		35% (21- 49)	70%* (57 – 82)	33% (7-60)	41% (33-50)

*significant difference (p<0.05) between children with and without PFV

Systemic disorders in children with PFV related cataract

5 of the 46 (11%) children with unilateral cataract associated with PFV were also affected by a non-ocular disorder or anomaly (table 2). These systemic abnormalities comprised: congenital toxoplasmosis, trisomy 21, haemophilia, and in two children for whom a formal diagnosis is awaited, lower intestinal and genitourinary malformations, and atrioseptal congenital cardiac anomaly. The child with congenital toxoplasmosis manifested complex PFV, whilst the other 4 children had isolated posterior hyaloid stalks.

Over half of the children, 7 / 12, with bilateral cataract and PFV had systemic disorders (table 3). 3 children had hereditary ocular or systemic disease, but for the majority of children with a systemic disorder a formal diagnosis or genotype has yet to be determined.

Outcomes following surgery for cataract associated with persistent fetal vasculature

All children with persistent fetal vasculature underwent primary surgery involving anterior capsulotomy, lens aspiration, primary posterior capsulotomy and primary anterior vitrectomy. Patent hyaloid stalks underwent diathermy prior to stalk division. 16/46 unilateral PFV eyes (35%), and 4/12 eyes of children with bilateral PFV (33%) underwent primary IOL implantation. 1 year following surgery for unilateral PFV cataract, 24% of operated eyes had achieved vision within normal range for age (95% CI 12-36) and 10% had only perception of light vision or worse (CI 1-19%). The proportion children with bilateral PFV cataract achieving normal vision in the better eye or with both eyes open was 20% (CI 0-43%) and all children had vision better than perception of light. The subgroup of children with complex PFV achieved

relatively poorer outcomes. No child with optic nerve head or retinal involvement achieved vision within the normal range for age 1 year after surgery, compared to 35% (CI 20-47%) of children with unilateral PFV not affecting the fundus.

No child with congenital cataract related PFV was diagnosed with glaucoma pre-operatively, and during the first post-operative year secondary glaucoma was diagnosed in 4% of children with unilateral (n=2, 95% CI 0-10%) and 9% with bilateral PFV cataract (n=1, 95% CI=0-15%). Of the two unilateral cases which developed secondary glaucoma, one had a posterior plaque only, the other a plaque and stalk. The bilateral cases had posterior plaque only. The frequency of post-operative glaucoma was not higher for eyes with anterior manifestations of PFV in either bilateral or unilateral cataract.

Table 3. Details of persistent fetal vasculature manifestation, identified aetiology and systemic disorders in bilaterally affected children

	Right eye manifestation	Left eye manifestation	Systemic disorder / anomaly and final diagnosis
1	PTVL – bilateral plaque		Dysmorphia, congenital arterioseptal defect, cleft palate, no formal diagnosis
2	PTVL – bilateral plaque and hyaloid artery		Macrocephalus, no formal diagnosis
3	ATVL – bilateral iris and anterior capsule remnant		WAGR Chromosome 11 deletion
4	ATVL – bilateral congenital pupillary membrane		Dysmorphia, hypospadias, no formal diagnosis
5	PTVL & ATVL – bilateral plaque and iris remnants		Neonatal frontal lobe infarct
6	PTVL – plaque	PTVL & ATVL – plaque and iris remnants	Cerebral atrophy, no formal diagnosis
7	PTVL – plaque	PTVL & ATVL – plaque, hyaloid artery and iris remnants	Congenital facial palsy

PTVL: Posterior tunica vasculosa lentis

ATVL: Anterior tunica vasculosa lentis

WAGR: Wilms tumour Aniridia Genitourinary Retardation syndrome

Discussion

We have found that the proportion of children who undergo surgery for congenital cataract associated with PFV is significantly higher than previously reported, even allowing for the widening of the definition of PFHV from that of PHPV. 42 of the 95 children with unilateral cataract (44%) within this present cohort would previously have been diagnosed with persistent hyperplastic primary vitreous, which remains a significantly higher proportion. This is unlikely to reflect a 'true' increase in the incidence of PFV, as such a rise would require a dramatic biological influence. Instead, our findings suggest that there is improved clinical recognition of the signs of persistent fetal vasculature. Furthermore, features of PFV may only be visible during removal of the cataractous lens, and children with persistent fetal vasculature may present earlier in life. Thus a study which recruits children undergoing surgery in early life may report a higher frequency of affected children. An Austrian study which prospectively recruited 31 children aged 0 – 15 years old with unilateral cataract reported that all had some feature of persistent vasculature.(7) Two large scale population based studies have described PFV as only affecting a relatively low proportion of children with cataract. Rahi et al reported that 22% of children aged 0 - 15 years diagnosed with unilateral congenital or infantile cataract in a national study were affected by PFV,(9) and investigators in Toronto reported the frequency to be 11% in children aged under 16 years at surgery for unilateral cataract.(10) These study populations described children diagnosed at any age with congenital and infantile cataract. This difference from the IoLunder2 study may partly explain the observed differences in frequency of PFV, as children with PFV manifestations may be diagnosed earlier than those without. The converse was, however, true for the

loLunder2 cohort where PFV was associated with later diagnosis in bilateral cataract.

36% of children with bilateral cataract, and 20% of those with unilateral cataract within the loLunder2 cohort achieved normal vision for age within the operated eye one year following surgery.(8) For the majority of children with congenital cataract associated with PFV, there is no evidence of worse outcome when compared to reported outcomes for the wider group of children within the loLunder2 cohort. Other investigators have theorised that the ocular maldevelopment secondary to failure of vascular regression results in worse functional and structural outcomes,(1;5) with worse vision for affected children and higher rates of post-operative glaucoma, and previous studies have reported a higher rate of pre and post-operative complications in eyes affected by PFV,(6) but within loLunder2 the only association with poor outcome was for those with optic nerve head or retinal anomalies in association with PFV. Congenital and infantile cataract per se are reflections of significant insult to lens development, and it may be that there is no 'summative' negative impact from the additional presence of persistent vasculature. The early outcomes from loLunder2 should be broadly predictive of later outcomes,(11) although more cases of post-operative glaucoma are likely to emerge.(12)

Stretched ciliary processes were once considered pathognomic for PFV,(3) but are now known to be present in other vitreoretinopathies such as retinopathy of prematurity or vitreoretinal dysplasia.(1) Our findings suggest that children with bilateral PFV are less likely to have ciliary traction, but also more likely to have anterior segment manifestations, and more likely to have a non-ophthalmic disorder, but the significance of this is unclear. There may be different pathogenetic pathways

involved for children with bilateral and unilateral disease. Emerging evidence suggests that in the majority of children affected by bilateral congenital and infantile cataract where there is no obvious associated 'syndrome', it is possible to identify a plausible pathogenic single gene mutation.⁽¹³⁾ The aetiology of PFV is poorly understood, but animal models have identified a role for the failure of both the macrophage orchestrated extrinsic apoptotic pathway⁽¹⁴⁾ and the tumour suppressor gene intrinsic apoptotic pathway⁽¹⁵⁾ in the pathogenesis of the persistence of the nutrient fetal vasculature. One gene complex implicated in the failure of ocular fetal vasculature apoptosis via the intrinsic pathway is *frizzled/wnt*⁽¹⁶⁾, which codes for a transmembrane protein. This protein is also implicated in the allelic congenital human retinal vascular development disorders of Norrie disease and familial exudative vitreoretinopathy, with the latter being described clinically as a 'hereditary form of retinopathy of prematurity (ROP)'. It has also been suggested that PFV is a result of failure of apoptosis due to reduced exposure to VEGF. This pathway has been supported by the changing patterns of VEGF receptors on mammalian fetal intraocular vasculature,⁽¹⁷⁾ and is a pathway of current clinical interest due to the use of VEGF inhibitors as treatment for ROP.

Primary prevention of unilateral cataract is an important goal as visual outcomes for unilateral remain poor. Understanding the aetiology and pathogenesis of PFV may contribute to this aim, and may increase the understanding of the vascularisation of the fetal retina and possibly of the entire fetal cerebral system. PFV is thus a worthy candidate for future genetic research but will require meticulous 'phenotyping', ie detailed description of morphology with pre-operative clinical imaging, ahead of investigation into genetic markers of the disorder.

Prompt diagnosis affording prompt treatment remains the most important management intervention for achieving good visual outcomes in congenital and infantile cataract. The early age at diagnosis for the majority of children with PFV related congenital cataract can be considered as an indicator of the success of the UK's ocular anomaly screening programme. Children undergo a red reflex test within 72 hours of birth, and a second examination with their general practitioner (family doctor) as part of the 6-8 week infant physical examination screening. However, this cohort consists only of children who have undergone cataract surgery. There may be a small number of children who did not undergo cataract surgery as late diagnosis had resulted in amblyopia sufficiently dense to be unlikely to respond successfully to treatment. 6 children (50%) with bilateral PFV cataract were diagnosed after 8 weeks of age. It is unclear whether these represent cases of 'late' diagnosis, or whether cases were diagnosed at a later age following progression of PFV related lens opacity.

The IoLunder2 study is able to provide population level data on the prevalence and manifestations of persistent fetal vasculature within children undergoing surgery for congenital and infantile cataract in the first two years of life, better informing clinicians on the characteristics and outcomes of this complex and uncommon disorder. On going follow up of this cohort will provide natural history and outcomes for children who have undergone surgery for PFV related cataract.

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Titles and legends to figures

E-supplement). The intraocular fetal vasculature

This anastamotic nutrient network disappears by full term birth.

Figure 1a and 1b. Relative frequencies and patterns of manifestation of the different features of PFV in a) unilateral and b) bilateral cataract

What was known before

Persistent fetal vasculature may affect a fifth of children with unilateral congenital or infantile cataract

Persistent fetal vasculature may be associated with poorer outcomes for babies and infants with cataract

What this study adds

Almost half of all children who undergo surgery unilateral congenital and infantile cataract, and a tenth of those with bilateral cataract have PFV

Positive family history is an uncommon finding in unilateral PFV related cataract

Most children with bilateral PFV also have a non-ophthalmic disorder

Outcomes, particularly in unilateral cataract, are similar for children with or without PFV