



# Shining a light on foveal development after congenital cataract surgery

Annegret Dahlmann-Noor<sup>1</sup>, Maryse Bailly<sup>2</sup>

<sup>1</sup>Department of Paediatric Ophthalmology, NIHR Moorfields Biomedical Research Centre, London, UK; <sup>2</sup>Department of Cell Biology, Institute of Ophthalmology, University College London, UK

*Correspondence to:* Annegret Dahlmann-Noor. Paediatric Service, Department of Paediatric Ophthalmology, NIHR Moorfields Biomedical Research Centre, 162 City Road, London EC1V 2PD, UK. Email: Annegret.dahlmann-noor@nhs.net.

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Cataract is the leading cause of treatable blindness in children in some developing countries, and one of the main leading causes worldwide; around 4 in 10,000 children are born with cataract (1,2). Whilst in adults, cataract surgery and implantation of an intraocular lens implant are highly successful, restoring sight and quality of life for millions of people every year, outcomes of cataract surgery in children are often poor. Early intervention is paramount to prevent permanent sight impairment from lack of input from the operated eye to the visual cortex (amblyopia)—if surgery is carried out later than a few weeks after birth, the brain will have lost its ability to develop high-resolution vision (3). However, the earlier surgery is performed, the higher the risk of another sight-threatening condition, glaucoma—progressive damage to the optic nerve from raised pressure in the eye (4). Given common delays in diagnosis and surgery and the risk of post-operative glaucoma, it may not be surprising that vision often remains poor despite successful surgery and intensive amblyopia management (5). Outcomes are even worse in children born with a cataract in only one eye, as the asymmetrical visual input to the brain is considered to invariably lead to amblyopia (6).

What might explain these poor outcomes? One possibility could be the difference in spectacle prescription between the healthy and the operated eye, leading to amblyopia. During cataract surgery in adults, a lens implant with an optical power to give good unaided distance vision is selected. In infants, often no lens implant is inserted at the time of cataract removal, as the eye is too small,

and to reduce the risk of post-operative adverse events. Postoperative optical management consists of contact lenses and glasses. When a lens implant is inserted, whether at the time of cataract removal or at a later stage, estimates are made to compensate for the anticipated growth of the eye during childhood and adolescence. Children therefore need regular sight tests to optimise their contact lens or spectacle prescription.

However, optical differences between the two eyes do not explain why the acuity in the operated eye remains poor. Amblyopia caused by the difference between the two eyes is often considered the main reason, though it should be possible to overcome underutilisation at the level of the visual cortex by intensive part-time patching of the healthy eye. As even intensive treatment does often not lead to normal vision, other factors may be relevant.

The part of the retina which provides high-resolution central vision and high visual acuity is the fovea, a depression in the central retina (macula) devoid of intraretinal blood vessels. Genetic and developmental disorders such as albinism affect foveal development and are typically associated with reduced visual acuity (7). Foveal development can also be affected by environmental factors, such as premature birth (7). Could congenital cataract affect the postnatal development of the fovea, compromising high-resolution acuity?

The normal development of the fovea is gradual, but three distinct phases can be distinguished (8): definition of the foveal avascular zone, foveal pit formation (depression

and widening), and foveal cone photoreceptor packing and differentiation. The first two phases occur before birth, with deepening and widening of the foveal pit continuing after birth, whilst cone packing and differentiation occur after birth.

In the first half of pregnancy, the fovea initially develops as an avascular zone with a single layer of photoreceptors (8). Local factors prevent both the migration of astrocytes into and the formation of intraretinal blood vessels within this central zone. Specifically, expression gradients in axon guidance factor EphA6 appear to regulate the rate and centrifugal migration of astrocytes, and gradients in anti-angiogenic pigment epithelium-derived factor (PEDF) expressed by retinal ganglion cells appear to suppress proliferation of endothelial cells in the foveal region (8).

Around week 25 gestational age, an intraretinal vascular ring starts to develop around the foveal avascular zone and indicates the beginning of foveal pit formation (8). The lack of retinal blood vessels makes the foveal region more deformable; finite element analysis suggests that pit formation results from rising intraocular pressure during the second half of pregnancy, continuing after birth (9). In addition, recent work suggests that Müller cells, a specialised type of support cell for retinal neurons, may be instrumental in pit formation. Foveal Müller cells appear to contract vertically and to exert tractional force onto their associated cone photoreceptors, leading to a depression in the foveal area (10). A specific underlying molecular pathway may involve *Arhgef33*, which regulates cytoskeletal dynamics associated with cellular contraction (11). From week 28 onwards, the foveal pit widens. Tractional forces, tangential retinal stretch from ocular growth (9), centrifugal displacement of retinal ganglion cells in the inner retina, and contraction of Müller cells around the fovea (10) have been implicated.

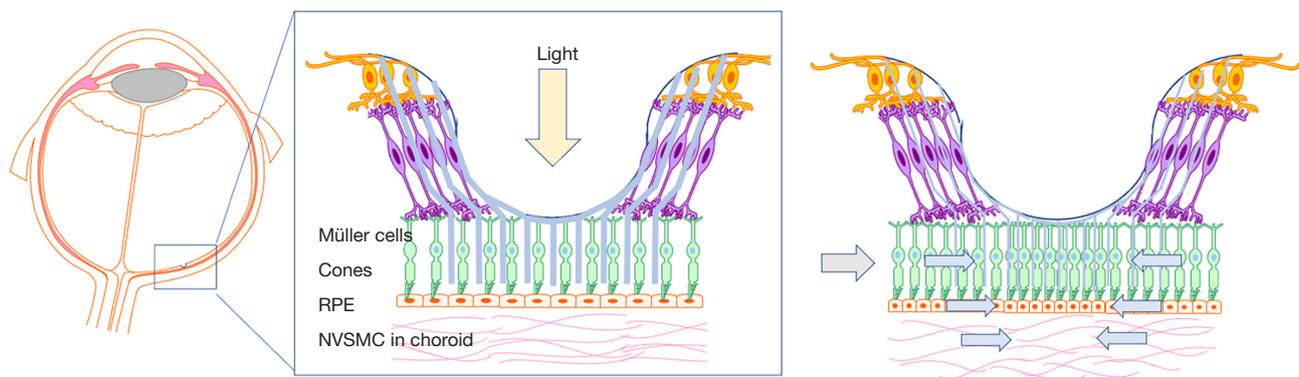
Shortly after birth, the third phase of foveal development begins, foveal cone photoreceptor packing and differentiation. This phase is triggered by and dependent on stimulation by light and results in the formation of visual images, though blurred (10). Lack of light and visual stimulation may affect cone packing, thereby precluding the development of high-resolution vision, even if the opacity is removed later (10).

In 2019, we published our observation of foveal underdevelopment in eyes which had undergone early childhood cataract surgery, compared with healthy eyes and eyes with cataract that had not undergone surgery (12). Our cross-sectional study reported that in operated eyes, the foveal

pit depth was reduced and that the subfoveal choroid, a layer dense in blood vessels which is the sole provider of oxygen and nutrients for the foveal cone photoreceptors and support cells, was thinner (12). This finding raised the possibility that congenital cataract may affect foveal and choroidal development, and that these could not be restored even with successful surgery. The observation of more severe reductions in post-surgical eyes compared with unoperated eyes may have been caused by selection bias, with more severe lens opacities having a higher likelihood to be operated on than partial cataracts which are expected to have a lesser impact on visual development (12). In 2020, a second team of clinicians confirmed foveal and choroidal underdevelopment after surgery for congenital cataract, associated with reduced visual acuity (13). A further study reported thinner subfoveal choroid in newborns with diverse conditions with foveal immaturity (14).

In this issue of *Annals of Translational Medicine*, Zhou *et al.* present additional detail about foveal development in children with unilateral congenital cataract who have undergone surgery, focusing on the choroid (15). Using high-resolution optical coherence tomography, the authors analysed not only the overall thickness and area of the subfoveal choroid, but also luminal and stromal area and choroidal vascularity index, differentiating vascular and stromal components (15). The contralateral eyes served as control. All choroidal parameters were smaller in eyes after congenital cataract surgery than in healthy controls. Importantly, the difference between operated eyes and healthy controls was driven exclusively by those eyes which before surgery had had dense/total cataracts; in those which had had partial cataracts, the measurements were no different to healthy controls [Tab. S2, (15)]. This is consistent with our finding that eyes that had undergone surgery, in our cohort those with more severe cataract, had worse foveal and subfoveal choroidal morphology. It may not be surprising that total cataracts, which reduce light and clarity of visual information more severely than partial cataracts, may have a greater impact, but until now, the main impact was considered to occur at the level of the visual cortex. Zhou *et al.*'s study adds to the body of evidence indicating impact on foveal development, with a downstream effect on visual cortex development.

Zhou *et al.* also noted that poorer visual acuity was associated with smaller choroidal parameters, linking choroidal morphology with visual function (15). The most likely explanation is that foveal cone photoreceptor packing and maturation were severely disrupted by total



**Figure 1** Proposed postnatal mechanisms of cone packing. Light (yellow arrow) may trigger radial contraction of cone photoreceptors inner segments (light green), horizontal contraction of Müller cells (light blue block lines), contraction of RPE cells (light orange) and/or choroidal NVSMCs (pink lines), thereby increasing foveal cone density. Molecular mechanisms may include light-triggered release of growth factors, cytokines and angiogenic factors by photoreceptors and RPE cells. Congenital cataract may impact on foveal cone packing and maturation by disrupting these pathways. Diagrams drawn using Motifolio Biomedical Diagrams. RPE, retinal pigment epithelial; NVSMCs, non-vascular smooth muscle cells.

cataract in the immediate period after birth, and that surgery, which probably took place before or around the time of school entry [in our study, median age at surgery for unilateral cataract was 4 months, interquartile range 1.3 to 52.1 months (12)], could not correct this defect.

Particular strengths of this publication are the narrow inclusion criteria for participants, excluding other eye pathology and including only unilateral isolated cataracts treated by surgical removal with insertion of a lens implant, followed by optical optimisation with spectacles. An additional strength is the inclusion of axial length measurements—higher axial length is often associated with a reduction in subfoveal choroidal thickness, and Zhou *et al.* are able to present here that this factor does not contribute to choroidal changes after childhood cataract surgery. Another confounding factor, diurnal variation of choroidal thickness, was equally factored in (15). The cross-sectional study design remains a limitation and precludes the conclusion that congenital cataract or surgery causally affect postnatal foveal development. A longitudinal study acquiring OCT images before or during surgery and then at regular intervals during optical optimisation and amblyopia treatment would be desirable to explore foveal maturation and subfoveal choroidal development.

Mechanical and molecular mechanisms of postnatal foveal cone packing and maturation and choroidal development are poorly understood. Prior studies suggest a clear link between light exposure after birth and normal foveal development, and our and Zhou *et al.*'s studies imply

that postnatal foveal pit deepening and development of subfoveal choroid are also affected by a lack of light.

How might light exposure in a short time window promote the development of these different tissues, and how might congenital cataract and light reduction prior to surgery interfere with these processes?

Proposed mechanisms underlying cone packing include radial contraction of cone inner segments and horizontal contraction of Müller cells (10). Light may be the stimulus triggering radial cone segment contraction, and stretching of their associated Müller cells may trigger release of growth factors which would further stimulate radial cone segment contraction (10). Alternatively, cone packing may be mediated by light-induced contraction of the foveal retinal pigment epithelial (RPE) layer and/or developing non-vascular smooth muscle cells (NVSMCs) in the subfoveal choroid (Figure 1). Evidence for contractility of RPE cells mostly comes from studies investigating fibrosing vitreoretinal conditions such as epiretinal membranes and proliferative vitreoretinopathy. RPE cells contain circumferential microfilament bundles, which contain typical contractile cytoskeletal proteins such as actin, myosin II, and tropomyosin (16,17). In RPE cell cultures, contraction is triggered by soluble growth factors and cytokines (18,19). The photoreceptors are tightly connected to the apical side of the RPE cells and thus could be physically moved closer upon contraction of the RPE layer, leading to packing. Indeed, there is evidence that RPE cells at the foveal area are smaller, more homogenous and more

densely packed than in parafoveal areas (20).

In addition, the choroid under the fovea and around the optic nerve head contains a dense network of NVSMCs (21). Their contraction has been implicated in moving the retinal plane forward to maintain a focused image during accommodation, the change from distance to near focus (21,22). The appearance of the contractile NVSMCs in the subfoveal choroid appears to coincide with exposure to light, suggesting a potential link. Whether contraction of subfoveal NVSMC contributes to photoreceptor packing is an intriguing question.

RPE cells secrete angiogenic vascular endothelial growth factor required for choroidal maintenance (23). Lack of light in the presence of a congenital cataract may disrupt RPE contraction and growth factor release, thereby compromising growth signals to the choroid. In turn, as proposed by Zhou *et al.*, choroidal underdevelopment may compromise the supply of oxygen and nutrients to foveal cones, further compromising vision (15). Conversely, lack of metabolic demand from underdeveloped photoreceptors may be associated with choroidal thinning, as seen in retinal dystrophies (24). Further longitudinal studies and fundamental science experiments are needed to explore the timeline of events and underlying mechanisms and the resulting question of whether light therapy from birth until cataract surgery can be performed may enhance foveal development and improve visual outcomes.

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