Acta Ophthalmologica

Early light deprivation effects on human cone-driven retinal function

Paolo Esposito Veneruso,[1] Lucia Ziccardi,[2] Giulia Magli,[1] Vincenzo Parisi,[2] Benedetto Falsini[3] and Adriano Magli[4]

[1]GI.MA Eyecare Centre, Naples, Italy
[2]"G.B. Bietti" Foundation – IRCCS, Rome, Italy
[3]Department of Ophthalmology, Catholic University of Rome, Rome, Italy
[4]Department of Pediatric Ophthalmology, University of Salerno, Salerno, Italy

ABSTRACT.

Purpose: **To assess whether the early light deprivation induced by congenital cataract may influence the cone-driven retinal function in humans.**

Methods: **Forty-one patients affected by congenital cataract (CC) who had undergone uncomplicated cataract extraction surgery and intraocular lens implant, and 14 healthy subjects (HS) were enrolled. All patients underwent complete ophthalmological and orthoptic evaluations and best-corrected visual acuity (BCVA) measurement; light-adapted full-field electroretinograms (ERG) and photopic negative responses (PhNR) were recorded to obtain a reliable measurement of the outer/inner retinal function and of the retinal ganglion cells' function respectively.**

Results: **Mean values of light-adapted ERG a- and b-wave and PhNR amplitude of CC eyes were significantly reduced and photopic ERG b-wave implicit time mean values were significantly delayed when compared to HS ones. When studying photopic ERG mean amplitudes at 5 ms, significant differences were found when comparing CC and control eyes. In CC eyes, statistically significant correlations were found between a- and b- wave amplitudes and PhNR amplitudes. No significant correlations were found between ERG parameters and BCVA, as well as between the age of CC patients at surgery and the time elapsed from lens extraction. No significant differences were found when functional parameters of bilateral and unilateral congenital cataract (uCC) eyes were compared, however uCC eyes showed significant differences when compared with contralateral healthy eyes.**

Conclusion: **We found a significant impairment of cone-driven retinal responses in patients with a history of congenital cataract. These changes might result from the long-lasting effects of early light deprivation on the cone retinal pathways. Our findings support the relevance of retinal involvement in deficits induced by early light deprivation.**

Key words: congenital cataract – electroretinogram – light deprivation – photopic negative response – retinal development – retinal function

Acta Ophthalmol. 2017: 95: 133–139

doi: 10.1111/aos.13191

Introduction

Early light deprivation induces anatomical and functional abnormalities at different levels of the visual pathways, confirming the important role of the sensory experience on the visual system development.

While cortical cells' unresponsiveness and lateral geniculate nucleus (LGN) abnormalities have been widely studied in vision-deprived animal models (Wiesel & Hubel 1963a; von Noorden & Crawford 1978), retinal involvement remains controversial. In experimental light-deprived primates, no significant differences have been found in retinal layer thickness or retinal ganglion cells' (RGCs) distribution between deprived and sound eyes (von Noorden 1973), and moreover, a normal scotopic electroretinogram (ERG) has been reported (Wiesel & Hubel 1963b; von Noorden et al. 1970). By contrast, an abnormal retinal function has been recorded in monocular light-deprived kittens (Ganz et al. 1968) and adult cats (Baxter & Rissen 1961; Babkoff 1975) and, in dark-reared mice, more recent studies (Dunn et al. 2013) have shown a selective decrease in the population of cone ON bipolar cells.

Although several studies have been performed in dark-reared animals, there is a lack of exhaustive information about the effects of light deprivation on the retinal function in humans.

The presence of congenital cataract represents a reliable human model of light deprivation, and so far, only few studies have been conducted which evaluate the retinal function by electrophysiological methods in patients with congenital cataract.

By using the standard ERG recordings, Yinon & Auerbach (1974) found a

slight reduction of light- and dark-adapted ERG b-wave amplitudes in 16 visually deprived children (nine from unilateral or bilateral congenital cataracts, five from traumatic cataracts and two from leukoma), while Zetterström (1974) studied the ERG parameters before and after cataract surgery, finding normal values of retinal function in 72.8% eyes, and subnormal values in only 14.9% of the total examined population (114 eyes), 5.2% of which was nonrecordable.

Full-field ERG recordings allow noninvasive evaluation of the cone outer retinal function (Hood & Birch 1995; McCulloch et al. 2015); by using specific stimulation settings, it is possible to study the slow negative potential displayed after the positive b-wave peak. This signal has been identified as the photopic negative response (PhNR) and has been studied as a probe of the inner retina function and, indirectly, of the RGCs' bioelectrical activity (Viswanathan et al. 1999; Colotto et al. 2000). The technique has shown high diagnostic accuracy in detecting inner retinal dysfunction in the paediatric setting (Abed et al. 2015).

In the present study, we aimed to assess whether early light deprivation induced by congenital cataract may influence the cone-driven retinal function in humans.

Subjects and Methods

Subjects

Forty-one patients, 20 males and 21 females, previously affected by total congenital cataract (defined as lens opacity present at least before 6 months of age) were enrolled. All patients had undergone an uncomplicated cataract surgery procedure with intraocular lens (IOL) implant (see below) before inclusion in the study. The mean age at testing was 10.6 ± 4.5 years (age ranging from 4.5 to 18.6 years).

The cataract extraction and IOL implant were performed in both eyes in 17 patients and only in one eye in 24 patients. Therefore, a total number of 58 eyes were included in the study (Congenital Cataract eyes – CC group).

Fourteen healthy age-similar (mean age: 11.0 ± 4.79 years, age range: 5.1–18.4 years) subjects served as controls (28 Healthy Subjects eyes – HS group).

Congenital cataract and HS underwent extensive ophthalmologic and orthoptic characterization, including best-corrected visual acuity (BCVA) measured with the Early Treatment Diabetic Retinopathy Study (ETDRS) charts, expressed as a logarithm of the minimum angle of resolution (logMAR), slit-lamp biomicroscopy, intraocular pressure (IOP) measurement, indirect ophthalmoscopy, retinoscopy (after cycloplegy with 1.0% atropine administration: two drops daily for 4 days), Hirschberg test, cover and cover-uncover test, Lang's stereotest, Worth's 4 light test and electrophysiological asessment by photopic ERG recordings (Retimax, CSO, Firenze, Italy).

Congenital cataract eyes were selected from a large cohort of patients of approximately 230 eyes that were affected by congenital cataract on the basis of the following exclusion criteria: presence of retinal (i.e. oedema, dystrophy, atrophy, retinopathy of prematurity), corneal or optical media disease (i.e. opacities, oedema), ocular abnormalities (i.e. microphthalmos, posterior-type persistent hyperplastic primary vitreous, persistent fetal vasculature), history of congenital glaucoma or systemic disorders able to influence learning ability, postoperative complications (i.e. retinal detachment, macular oedema, ocular inflammation), myopic or hyperopic refractive error greater than 3.50 dioptre (spherical equivalent), postoperative glaucoma and cataract morphology different from the total one (i.e. lamellar, posterior subcapsular, polar). Total congenital cataract was defined based on the absence of fundus red reflex (Haargaard et al. 2015) and the presence of dense, white cortico-nuclear opacity extending from the nucleus of the lens up to the zonular fibres' insertion at least before 6 months of age. This was confirmed through a thorough eye examination under sedation performed by the same eye examiner (A.M.) for each evaluated eye.

Healthy subjects were selected using the following parameters: presence of orthotropia, IOP lower than 18 mmHg, BCVA equal or less than −0.18 LogMAR, absence of diseases involving anterior segment, retina or optic nerve, no history of previous ocular or systemic disease and no previous ocular surgery.

In all CC eyes, surgical procedures consisting of mechanical anterior capsulorhexis, manual or automated extracapsular lens extraction, posterior capsulorhexis or posterior capsulotomy and central anterior vitrectomy were performed under general anaesthesia by the same experienced surgeon (A.M.). Antibiotics were postoperatively injected into the anterior chamber and dexamethasone was injected subconjunctivally after surgery (Magli et al. 2013, 2015). All patients underwent primary implant of the IOL at the time of lens removal.

Table 1 presents demographic and clinical data of our patients: mean age and standard deviations (SD) from CC and from HS patients; mean age of surgery for CC patients; additional and ocular motility disorders are also reported.

Each CC patient was clinically examined at several time-points after surgery: 2 days, 1 week, 2 weeks, 1 month, 3 months and then every 4 months after surgery. Occlusion therapy was prescribed postoperatively to all patients (1 hr per month of age daily for a maximum of 6 hr). Patients interrupted occlusion therapy at the age of 12 years; at the time of the examination patients younger than 12 years were receiving occlusion therapy of dominant eyes. Congenital cataract (CC) enrolled eyes in the present study underwent clinical and electrophysiological assessment on

Table 1. Demographic data in healthy subjects and patients with history of congenital cataract.

	n eyes	Age (mean ± SD)	Age of surgery (mean ± SD)	Additional surgery	Motility disorders
HS	28	11.0 ± 4.8	–	–	–
CC	58	10.6 ± 4.6	1.6 ± 1.4	2 IOL substitution 5 strabismus 3 IOL dislocation	9 nystagmus 15 exodeviation 15 esodeviation 15 hypertropia

HS = healthy subjects, CC = patients with history of congenital cataract, SD = standard deviation; IOL = intraocular lens.

average 9.1 ± 4.2 years after cataract removal.

The study followed the tenets of the Declaration of Helsinki and an informed consent to participate in the study was obtained from all subjects, or their parents, after full explanation of the aims and modalities of the investigation. Institutional Review Board (IRB) approval was obtained.

Electrophysiological recordings

Congenital cataract (CC) and HS eyes underwent full-field ERG recordings. To enhance the examined young patients' (4.5 years of age) compliance thus excluding the effects of sedative drugs on ERG recordings (Whitacre & Ellis 1984; Tanskanen et al. 1996), and in order to obtain more reliable measurements, light-adapted ERG and PhNR recordings were performed in two separate sessions within 1 week using skin electrodes (Colotto et al. 2000; Abed et al. 2015).

Electroretinograms recordings were obtained from both eyes, after full pupil dilatation by instillation of two drops of 1% tropicamide (the second drop after 10 min from the first one). Pupils were central and round, with a diameter measuring ≥7 mm in all patients and no anisocoria was found. Following the ISCEV standards (McCulloch et al. 2015), photopic ERGs were recorded (Retimax, CSO) in response to Ganzfeld flash stimulation after 10 min of preadaptation to a steady background of 30 cd/m^2. Consequently, white 50 ms stimuli with an intensity of 3 cd/m^2 were presented on a steady white background of 30 cd/m^2. The interstimulus interval was 1 second. Electroretinograms (ERGs) were recorded by skin electrodes following a paediatric protocol first proposed by Fulton et al. (2006) and adopted in the paediatric setting (Abed et al. 2015).

Silver chloride electrodes (0.8 mm) were taped on the skin of the lower eyelids, just 2.5 mm below the inferior lid rim, in the vertical axis passing through the corneal apex. An interocular reference was used (Fiorentini et al. 1981) to minimize the noise coming from blink and conjugate eye movement artefacts.

Signals were amplified (50 K), filtered (0.3–300 Hz), digitized at 2 KHz, and averaged (40 events) with automatic artefact rejection. Forty events for each run were collected. Two runs were typically performed for each eye. The peak-to-peak noise level was estimated in line with the sum of events and odd events obtained for the averaging process.

After obtaining conventional light-adapted ERGs, all subjects underwent specific protocol for PhNR recordings, previously published by Abed et al. (2015). In brief, the patient was adapted to a steady background of 20 cd/m^2 for 10 min, and thereafter ERGs were recorded in response to Ganzfeld flash stimulation. White 50-ms stimuli with an intensity of 2 cd/m^2 were presented on the steady white background (20 cd/m^2). The interstimulus interval was 1 second.

Light-adapted ERG a-wave amplitude was measured from prestimulus baseline to first negative trough; the amplitude of the a-wave at 5 ms after the light stimulus presentation was also measured in order to indirectly isolate cone photoreceptors' contribution to the ERG (Robson et al. 2003; Friedburg et al. 2004). The photopic ERG b-wave amplitude was measured from the negative peak of the a-wave to the positive peak of the b-wave, and the PhNR amplitude was measured from the prestimulus baseline to the most negative trough following the b-wave (see Fig. 1).

Statistics

A two-tailed unpaired *t*-test was performed to compare ERG a- and b-wave amplitudes and implicit times, and PhNR amplitudes between groups (HS and CC eyes). Test–retest results from CC and HS eyes (one randomly selected eye for each group was included in the analysis) were evaluated by calculating the absolute and percentage amplitude difference between the two test results (i.e. first–second test) for each patient. The coefficient of repeatability was estimated according to the methods reported by Fleiss (1999) and Bland & Altman (1999). For all parameters, 95% confidence limits were obtained from age-similar normal subject data by calculating mean values minus and plus 2 standard deviations (SD). Mean values +2 standard deviations were calculated for ERG a- and b-wave implicit times (upper limit) and mean values −2 standard deviations for ERG a- and b-wave and PhNR amplitudes (lower limit). Pearson's correlation was applied in order to examine a possible association between electrophysiological parameters and BCVA data and the time elapsed from lens extraction surgery. For all analyses, a conservative p-value of <0.001, compensating for multiple correlations, was considered as statistically significant. The SAS statistical software package (version 9.1, SAS Institute Inc, Cary, NC, USA) was used.

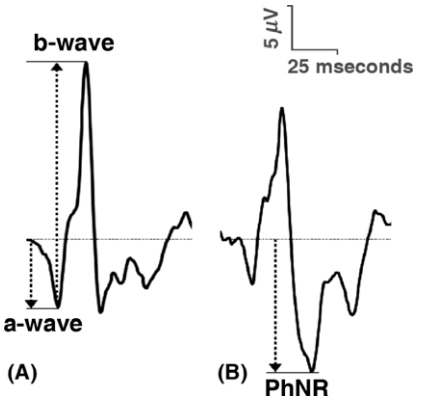

Fig. 1. Representative waveforms of the light-adapted electroretinogram (A), showing a- and b-wave amplitude (arrows) and implicit time (solid lines) values, and of the Photopic Negative Response (B) recordings from a control subject.

Results

Table 1 shows demographic data from our cohorts: healthy subjects and patients with a history of congenital cataract. Clinically, we assessed BCVA values and light-adapted ERGs and PhNR recording responses in all enrolled subjects from HS and CC groups. Layouts of light-adapted ERGs and PhNR recordings in a healthy eye from a control subject are reported in Fig. 1.

Representative examples of light-adapted ERG and PhNR signals recorded from HS, bilateral and unilateral CC eyes are displayed in Fig. 2.

Based on 95% confidential limits, CC group showed individual abnormal values of a- and b-wave peak time, in 10/58 and 12/58 eyes respectively and abnormal a-, b-wave and PhNR amplitudes in 5/58, 12/58 and 5/58 eyes respectively.

Table 2 shows mean values and relative SD of BCVA and mean

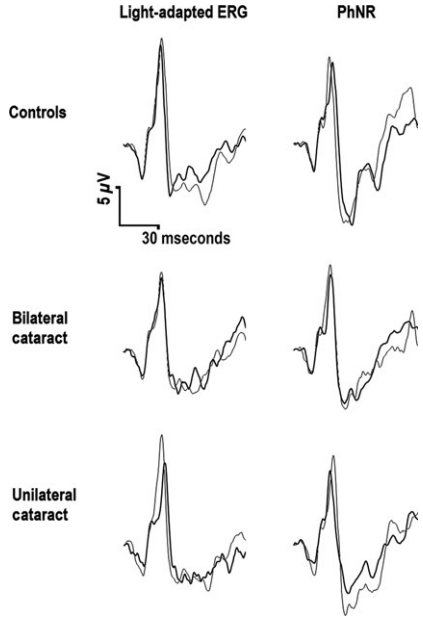

Fig. 2. Layouts of light-adapted electroretinogram (ERG) (left column) and photopic negative response (PhNR) (right column) waveforms from both eyes of a representative control subject, a patient with bilateral congenital cataract and a patient with unilateral cataract (the thicker line is from the affected eye).

light-adapted ERG a-, b- and PhNR wave amplitudes and implicit times for the three groups with the *t*-test results between groups. We also presented data from subjects with unilateral congenital cataract (uCC) discriminating between the affected and the unaffected eye (cHE: contralateral Healthy Eye).

On average BCVA values, light-adapted ERG a-, b- and PhNR amplitudes, and b-wave implicit times of all CC eyes were significantly different when compared to healthy eyes. Excluding the individual abnormal electrophysiological values from the statistical analysis, the significance of our findings was unvaried. No significant differences were found when all functional parameters of bilateral and unilateral congenital cataract eyes were compared (data not shown; $p > 0.17$); therefore, the functional responses of eyes affected by bilateral and unilateral congenital cataract were pooled together when performing the comparisons with HS eyes. Light-adapted ERG a- and b-wave and PhNR amplitudes and b-wave implicit times of uCC eyes showed significant differences when compared with those of the cHE ($p < 0.001$). No statistically significant differences were found when electrophysiological response parameters from contralateral healthy eyes in unilateral congenital cataract were compared to control ones (data not shown; $p > 0.35$). Table 2 also shows that mean amplitude values of light-adapted ERG a-wave measured at 5 ms in CC eyes were significantly different from those of the control group, whereas nonsignificant difference between mean values ($p = 0.009$) was found when comparing uCC and cHE eyes.

In Fig. 3, individual amplitude values of a-, b- and PhNR waves from CC eyes were plotted. We found highly significant correlations between all electrophysiological parameters ($p < 0.001$). When plotting mean values of BCVA as a function of electrophysiological parameters in CC and HS groups, no statistically significant differences were found. Also, no correlation was found between the age of CC patients at surgery, the time elapsed from lens extraction and BCVA and electrophysiological parameters (data not shown).

Discussion

Cone-driven retinal function in early light-deprived humans has been scarcely investigated. To investigate whether the cone system is functionally affected by early light deprivation, we studied the retinal function in one of the most reliable light deprivation models in humans: the congenital cataract. Thus, we recorded conventional light-adapted ERG and PhNR responses in young patients with a history of congenital cataract after surgical extraction and IOL implant (CC eyes).

We found that on average, when compared to controls, the light-adapted ERG (a- and b-wave and the a-wave measured at 5 ms) and PhNR amplitude values were significantly reduced in CC eyes. Similarly, the mean light-adapted ERG b-wave implicit times resulted significantly delayed. When considered together, these results suggest a functional impairment of cone-related retinal generators in the outer and inner layers in eyes with early light deprivation induced by congenital cataract.

Cone-driven retinal function: ERG a- and b-wave data

In detail, mean values of the light-adapted ERG a-wave amplitude were found to be reduced by approximately 30 and 35% respectively, in all (bilateral and unilateral) CC eyes when compared to controls (see Table 2). The light-adapted ERG a-wave is generally considered to reflect cone photoreceptors' activity, however,

Table 2. Clinical and electrophysiological measurements in healthy subjects and patients with history of congenital cataract.

	BCVA (mean ± SD)	Light-adapted ERG a-wave (mean ± SD)		Light-adapted ERG b-wave (mean ± SD)		PhNR (mean ± SD)	Light-adapted ERG a-wave measured at 5 ms (mean ± SD)
	LogMAR	Amplitude (μV)	Peak time (ms)	Amplitude (μV)	Peak time (ms)	Amplitude (μV)	Amplitude (μV)
HS (28 eyes)	−0.18	6.09 ± 2.01	15.73 ± 1.42	17.37 ± 4.20	32.16 ± 1.11	9.40 ± 2.47	3.96 ± 1,49
CC (58 eyes)	0.73 ± 0.63	4.13 ± 1.80	16.67 ± 2.52	12.19 ± 4.10	33.53 ± 1.60	6.95 ± 2.47	2.54 ± 1.04
CC versus HS	$p < 0.001$	$p < 0.001$	$p = 0.030$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
uCC (24 eyes)	0.91 ± 0.75	3.95 ± 1.40	16.23 ± 2.65	12.90 ± 3.21	33.22 ± 0.94	6.49 ± 2.01	2.66 ± 1.06
cHE (24 eyes)	0.00 ± 0.23	5.68 ± 1.81	15.66 ± 1.50	17.53 ± 5.15	32.39 ± 0.67	8.86 ± 2.37	2.91 ± 1.27
uCC versus cHE	$p < 0.001$	$p < 0.001$	$p = 0.32$	$p < 0.001$	$p = 0.015$	$p < 0.001$	$p = 0.009$

HS = healthy subjects; CC = patients with history of congenital cataract, BCVA = best-corrected visual acuity, ERG = electroretinogram, PhNR = photopic negative response, uCC = unilateral congenital cataract, cHE = contralateral healthy eye, SD = standard deviation.

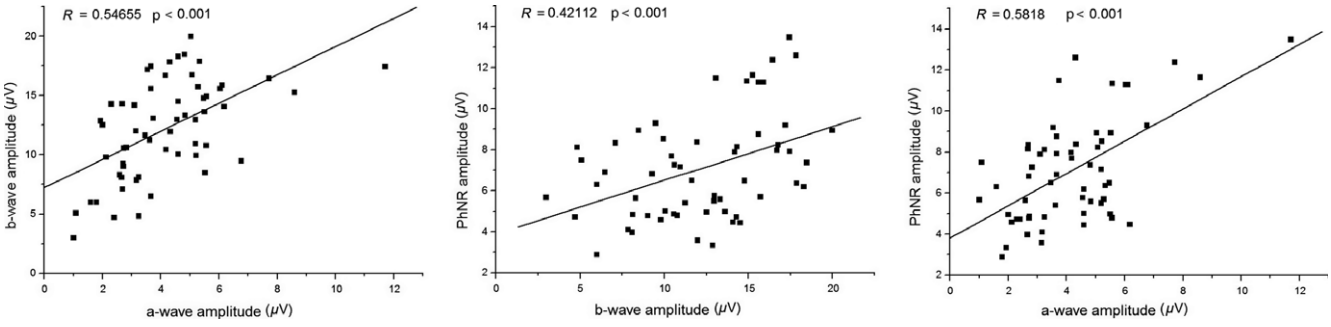

Fig. 3. Correlations between electrophysiological parameters in eyes with history of congenital cataract. Pearson's correlations (R and p-values) between light-adapted electroretinogram (ERG) a-, b-wave and photopic negative response (PhNR) amplitudes from eyes with history of congenital cataract are reported.

hyperpolarizing bipolar and/or horizontal cells might also contribute to the ERG a-wave genesis (Evers & Gouras 1986; Falk & Shiells 1986). Indeed, it has been shown that the photopic ERG a-wave origin is only for approximately two-thirds of the total amplitude, due to the cone photoreceptors' activity, and therefore the contribution by the postphotoreceptoral component is mostly appreciable (Bush & Sieving 1994; Friedburg et al. 2004). To select the cone photoreceptors' activity, we studied the amplitude of ERG a-wave at 5 ms (Robson et al. 2003; Friedburg et al. 2004) from the stimulus presentation; we found a statistically significant reduction of this parameter in CC eyes when compared to control ones, however no differences were found between unilateral CC and contralateral healthy eyes. These findings support the hypothesis of outer retinal dysfunction involving cone photoreceptors.

On average, when CC eyes were compared to control ones, significantly reduced photopic ERG b-wave amplitudes and delayed implicit times were also found. The cellular origin of the full-field photopic ERG b-wave has been widely studied: Sieving et al. (1994) proposed a push-pull model involving depolarizing-ON-bipolar, hyperpolarizing-OFF-bipolar and horizontal cells activity; the role for the extracellular potassium that reaches the Müller cells was also hypothesized and Shirato et al. (2008) reported a "positive intrusion" in the ERG due to bipolar, amacrine and ganglion activity.

Mice's cone photoreceptors connect with at least 10 different types of ON and OFF cone-bipolar cells (Wässle et al. 2009): the bipolar choice of synaptic cone partners can be settled upon before or after the eye opening (Dunn & Wong 2012). While dark-rearing has been reported to have no effect on responses of rod photoreceptors or rod bipolar cells in mice, it affects the development of cone contacts confirming that cone-to-cone bipolar contacts' development depends on sensory stimulation (Dunn et al. 2013). Also in light-deprived cats, Babkoff (1975) described a substantially normal photoreceptors' function and altered b-wave shaping at higher luminance stimuli. According to these findings on the effects of light deprivation in animals, the abnormal b-wave amplitudes and implicit times found in our CC eyes suggest that early visual deprivation also affects cone first synapse in humans. However, whether the impairment involves ON or OFF pathways needs to be clarified. We also reported delayed b-wave implicit times when CC eyes were compared to controls; to our knowledge b-wave implicit times in animal models of light deprivation has never been extensively investigated.

The fact that our patients underwent electrophysiological examination on average about 9 years after their surgery, which occurred at an average age of 1.6 years, implies that light deprivation occurs early in life and permanently affects the retinal cone-mediated function. These findings may also explain why often CC patients do not reach satisfactory visual psychophysical results despite several years of occlusion therapy.

RGCs function: PhNR recordings data

In the present study, we reported a significant reduction of the mean PhNR amplitudes in CC eyes when compared to control ones.

The cone-mediated ERG photopic negative response has been ascribed to RGCs and amacrine cells' function, thus reflecting the inner retinal activity (Bloomfield 1996; Viswanathan et al. 1999).

Notwithstanding the development of the higher visual brain centre which is known to continue for weeks after the eye opening (Katz & Shatz 1996; Issa et al. 1999), retinal structure has been considered to reach adult levels by the time of eye opening (Daw 1995). Studies of retinal development in lower species indicated that short-term visual deprivation did not have discernible effects on retinal morphology or on light-evoked responsiveness activity (Wiesel & Hubel 1963a,b; Hendrickson & Boothe 1976; Baro et al. 1990). On the other hand, there is evidence that dark-rearing alters the pruning and stratification process of RCGs dendritic trees (Bodnarenko & Jeyarasasingam 1995; Tian & Copenhagen 2003). Visual experience is also responsible for ON-OFF RGCs laminae stratification (Tian & Copenhagen 2001, 2003) and for the maintenance and plasticity of synaptic connection (Hooks & Chen 2006). In other words, it is likely that activity-driven refinement modulates genetically programmed circuits (Wang et al. 2001). Furthermore, recently, early visual deprivation was shown to produce permanent changes in the spontaneous synaptic activity recorded from rat RGCs (Giovannelli et al. 2008). Consistent with Giovannelli's considerations, our results of a reduced PhNR response in pseudophakic eyes, suggest that early visual deprivation has long-lasting effects on the RGCs' function.

We also found a strong correlation between light-adapted ERG a- and b-wave amplitudes. These findings suggest the existence of a strict functional relationship between cone pathways' elements in CC eyes. When plotting the PhNR amplitude values as a function of a- and b-wave amplitudes, we found a significant correlation, implying RGC dysfunction is the result of a reduced output from more distal retinal components in eyes.

Neurofunctional considerations

To the best of our knowledge, for the first time, the present results show significant differences in the retinal cone-driven function between eyes with congenital cataract history and healthy eyes, thus confirming the long-lasting effect of early light deprivation on retinal structures also in humans.

Our findings are consistent with cone-driven retinal dysfunction probably arising from the outer retinal layers; nevertheless rod-system involvement cannot be excluded.

The present work has several limitations and possible alternative factors influencing our findings need to be taken into consideration. For instance, (1) it is widely known that the use of skin electrodes achieves smaller ERG signals than corneal ones, therefore, for a more accurate measurement of the ERG a-wave amplitudes at 5 ms, corneal electrodes and appropriate stimulation paradigms should be used, (2) we were not able to verify and quantify the percentage of transmitted light trough opaque lenses in very young patients, (3) we could not exclude whether mechanical effects of surgery (even though without complications) influenced the retinal function and (4) the transmittance of artificial IOL or its effects on the absorption of ERG stimulus by retinal structure were not investigated.

Nevertheless, the effect of resistance of implanted IOL on light absorption by retina was not considered to be relevant, because it is reported as not having a significant effect on contrast retinal responses in adults (Porciatti et al. 1992). In addition, an international grading scale describing the density and/or the position of the congenital lens opacities in children is not yet available, hence, for this reason we chose to enrol only eyes affected by total cataract in the present study; this choice made our sample extremely homogeneous.

In conclusion, many studies have investigated the effects of light deprivation on the visual pathways, at the LGN and visual cortex levels in terms of morphological and functional abnormalities. In agreement with previous studies in animal models, our findings of the impairment of the cone-driven retinal function in patients previously affected by congenital cataract, support the relevance of retinal involvement in visual deficits induced by early light deprivation: human retinal function appears to be highly sustained by light stimulation.

References

Abed E, Piccardi M, Rizzo D et al. (2015): Functional loss of the inner retina in childhood optic gliomas detected by photopic negative response. Invest Ophthalmol Vis Sci **56**: 2469–2474.

Babkoff H (1975): The effect of light-deprivation on the adult electroretinogram. Vision Res **15**: 870–872.

Baro JA, Lehmkuhle S & Kratz KE (1990): Electroretinograms and visual evoked potentials in long-term monocularly deprived cats. Invest Ophthalmol Vis Sci **31**: 1405–1409.

Baxter BL & Rissen AH (1961): Electroretinogram of the visually deprived cat. Science **134**: 1626–1627.

Bland JM & Altman DG (1999): Measuring agreement in method comparison studies. Stat Methods Med Res **8**: 135–160.

Bloomfield SA (1996): Effect of spike blockade on the receptive-field size of amacrine and ganglion cells in the rabbit retina. J Neurophysiol **75**: 1878–1893.

Bodnarenko SR, Jeyarasasingam G & Chalupa LM (1995): Development and regulation of dendritic stratification in retinal ganglion cells by glutamate-mediated afferent activity. J Neurosci **15**: 7037–7045.

Bush RA & Sieving PA (1994): A proximal retinal component in the primate photopic ERG a-wave. Invest Ophthalmol Vis Sci **35**: 635–645.

Colotto A, Falsini B, Salgarello T, Iarossi G, Galan ME & Scullica L (2000): Photopic negative response of the human ERG: losses associated with glaucomatous damage. Invest Ophthalmol Vis Sci **41**: 2205–2211.

Daw NW (1995): Visual development. New York: Plenum Press.

Dunn FA & Wong RO (2012): Diverse strategies engaged in establishing stereotypic wiring patterns among neurons sharing a common input at the visual system's first synapse. J Neurosci **32**: 10306–10317.

Dunn FA, Della Santina L, Parker ED & Wong ROL (2013): Sensory experience shapes the development of the visual system's first synapse. Neuron **80**: 1159–1166.

Evers HU & Gouras P (1986): Tree cone mechanism in the primate electroretinogram: two with, one without off-center bipolar responses. Vision Res **26**: 245–254.

Falk G & Shiells RA (1986): Do horizontal cell responses contribute to the electroretinogram (ERG) in dogfish? J Physiol **381**: 113.

Fiorentini A, Maffei L, Pirchio M et al. (1981): The ERG in response to alternating gratings in patients with diseases of the peripheral visual pathway. Invest Ophthalmol Vis Sci **21**: 490–493.

Fleiss JL (1999): Repeated measurements studies. In: Shube B (ed.). The design and analysis of clinical experiments. New York: Wiley Interscience 220–232.

Friedburg C, Allen CP, Mason PJ & Lamb TD (2004): Contribution of cone photoreceptors and post-receptoral mechanisms to the human photopic electroretinogram. J Physiol **556**(Pt 3): 819–834.

Fulton AB, Brecelj J, Lorenz B, Moskowitz A, Thompson D & Westall CA (2006): ISCEV Committee for Pediatric clinical electrophysiology. Guidelines Pediatric clinical visual electrophysiology a survey of actual practice. Doc Ophthalmol **113**: 193–204.

Ganz L, Fitch M & Satterberg JA (1968): The selective effect of visual deprivation on receptive field shape determined neurophysiologically. Exp Neurol **22**: 614–637.

Giovannelli A, Di Marco S, Maccarone R & Bisti S (2008): Long-term dark rearing induces permanent reorganization in retinal circuitry. Biochem Biophys Res Commun **365**: 349–354.

Haargaard B, Nyström A, Rosensvärd A, Tornqvist K & Magnusson G (2015): The Pediatric Cataract Register (PECARE): analysis of age at detection of congenital cataract. Acta Ophthalmol **93**: 24–26.

Hendrickson A & Boothe R (1976): Morphology of the retina and dorsal lateral geniculate nucleus in dark-reared monkeys (Macacanemestrina). Vision Res **16**: 517–521.

Hood DC & Birch DG (1995): Phototransduction in human cones measured using the alpha-wave of the ERG. Vision Res **35**: 2801–2810.

Hood MP, Kerr NC, Smaoui N & Iannaccone A (2015): Abnormal cone ERGs in a family with congenital nystagmus and photophobia harboring a p.X423Lfs mutation in the PAX6 gene. Doc Ophthalmol **130**: 157–164.

Hooks BM & Chen C (2006): Distinct roles for spontaneous and visual activity in remodeling of the retinogeniculate synapse. Neuron **52**: 281–291.

Issa NP, Trachtenberg JT, Chapman B, Zahs KR & Stryker MP (1999): The critical period for ocular dominance plasticity in

the Ferret's visual cortex. J Neurosci **19**: 6965–6978.

Katz LC & Shatz CJ (1996): Synaptic activity and the construction of cortical circuits. Science **274**: 1133–1138.

Magli A, Forte R & Rombetto L (2013): Long-term outcome of primary versus secondary intraocular lens implantation after simultaneous removal of bilateral congenital cataract. Graefes Arch Clin Exp Ophthalmol **251**: 309–314.

Magli A, Forte R, Rombetto L & Magli G (2015): Long-term outcomes of primary intraocular lens implantation for unilateral congenital cataract. Semin Ophthalmol **21**: 1–6.

McCulloch DL, Marmor MF, Brigell MG, Hamilton R, Holder GE, Tzekov R & Bach M (2015): ISCEV Standard for full-field clinical electroretinography (2015 update). Doc Ophthalmol **130**: 1–12.

von Noorden GK (1973): Behavioral and anatomical aspects of experimental amblyopia in monkeys. Trans Am Ophthalmol Soc **71**: 111–123.

von Noorden GK & Crawford MLJ (1978): Morphological and physiological changes in the monkey visual system after short-term lid suture. Invest Ophthalmol Vis Sci **17**: 762–768.

von Noorden GK, Dowling JE & Ferguson DC (1970): Experimental amblyopia in monkeys. I. Behavioral studies of stimulus deprivation amblyopia. Arch Ophthalmol **84**: 206–214.

Porciatti V, Burr DC, Morrone MC & Fiorentini A (1992): The effects of aging on the pattern electroretinogram and visual evoked potential in humans. Vision Res **32**: 1199–1209.

Robson JG, Saszik SM, Ahmed J & Frishman LJ (2003): Rod and cone contributions to the a-wave of the electroretinogram of the macaque. J Physiol **547**(Pt 2): 509–530.

Shirato S, Maeda H, Miura G & Frishman LJ (2008): Postreceptoral contributions to the light-adapted ERG of mice lacking b-waves. Exp Eye Res **86**: 914–928.

Sieving PA, Murayama K & Naarendorp F (1994): Push-pull model of the primate photopicelectroretinogram a role for hyperpolarizing neurons in shaping the b-wave. Vis Neurosci **11**: 519–532.

Tanskanen P, Kylmä T, Kommonen B & Karhunen U (1996): Propofol influences the electroretinogram to a lesser degree than thiopentone. Acta Anaesthesiol Scand **40**: 480–485.

Tian N & Copenhagen DR (2001): Visual deprivation alters development of synaptic function in inner retina after eye opening. Neuron **32**: 439–449.

Tian N & Copenhagen DR (2003): Visual stimulation is required for refinement of ON and OFF pathways in postnatal retina. Neuron **39**: 85–96.

Viswanathan S, Frishman LJ, Robson JG, Harwerth RS & Smith EL 3rd (1999): The photopic negative response of the macaque electroretinogram: reduction by experimental glaucoma. Invest Ophthalmol Vis Sci **40**: 1124–1136.

Wang GY, Liets LC & Chalupa LM (2001): Unique functional properties of on and off pathways in the developing mammalian retina. J Neurosci **21**: 4310–4317.

Wässle H, Puller C, Müller F & Haverkamp S (2009): Cone contacts, mosaics, and territories of bipolar cells in the mouse retina. J Neurosci **29**: 106–117.

Whitacre MM & Ellis PP (1984): Outpatient sedation for ocular examination. Surv Ophthalmol **28**: 643–652.

Wiesel TN & Hubel DH (1963a): Effects of visual deprivation on the morphology and physiology of cells in the cat's lateral geniculate body. J Neurophysiol **26**: 978–993.

Wiesel TN & Hubel DH (1963b): Single-cell responses in striate cortex of Kittens deprived of vision in one eye. J Neurophysiol **26**: 1003–1017.

Yinon U & Auerbach E (1974): The electroretinogram of children deprived of pattern vision. Invest Ophthalmol **13**: 538–543.

Zetterström B (1974): The electroretinogram in congenital cataract. Acta Ophthalmol (Copenh) **52**: 342–348.

Received on January 12th, 2016.
Accepted on June 13th, 2016.

Correspondence:
Dr Adriano Magli, MD
GI.MA centro di diagnostica e terapia oculare
Via Mergellina, 44
80122 Napoli, Italy
Tel: +39 081 761 26 09
Fax: +39 081 66 43 73
Email: amagli@unisa.it