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PEDIATRICS

Developmental visual deprivation: long term effects on human cone driven retinal function

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Abstract
Purpose To assess whether infantile visual deprivation induced by developmental cataract may influence the cone-driven retinal function in humans.
Methods A total of 14 patients with history of bilateral developmental cataract (DC), 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 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.
Result Mean values of light-adapted ERG a- and b-wave implicit times were slightly delayed when compared to HS values. Light-adapted ERG a-wave amplitude mean values showed borderline values ($p = 0.001$), whereas a-wave amplitude analysis at 5 ms, b-wave and PhNR amplitude mean values showed no significant differences when compared to control values. No significant correlations were found when age at surgery, time elapsed from surgery, duration of the visual deprivation, age at examination, age at first detection of the opacity, BCVA and electrophysiological parameters were plotted together.

Coherently with morphological studies, the extremely light bioelectrical impairment of the cone pathway in our cohort of patients describes minimal functional abnormalities of a well-structured retina that is not completely mature.
Conclusions Our present results, combined to those of our previous work on congenital cataracts, allow us to enhance the comprehension of functional developmental mechanisms of children's retinas and highlight the relevance of the timely treatment of lens opacities during infancy.

Keywords Developmental cataract · Retinal function. · Visual deprivation. · PhNR. · Electroretinogram. · Retinal ganglion cells function.

Introduction

Childhood, pediatric and infantile cataract are terms indicating an opacity that occurs in the first years of life. In such cases, it is extremely important to discriminate between "developmental" and "congenital" cataracts, especially when the purpose is to study the effects of visual deprivation on retinal structures during development. Opacities present at birth or within the first 6–12 months of age are defined as "congenital" [1–3], while cataracts that form after 7–12 months of age are generally considered "developmental" [1, 3, 4]. This distinction is necessary considering the documented modifications of retinal structures occurring after birth in both animal and human models [5–8]. The existence of a post-natal retinal maturation process leads us to hypothesize that a given visual deprivation might lead to different forms of functional impairment depending on the time after birth at which it occurred, especially at early ages.

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Retinal function in early light-deprived patients affected by congenital cataract has been scarcely investigated [9–11] and, to our knowledge, no functional studies exist in patients with developmental cataract.

In the present study, we aimed to investigate the cone-driven retinal function in patients who were visually-deprived early in life by bilateral developmental cataracts.

Materials and methods

Fourteen patients (28 eyes) with history of bilateral developmental cataract, defined as lens opacity, occurring later than at least 1 year of life, were enrolled. We included only patients with at least one full negative examination (see below) before the opacity was noted. All patients had undergone an uncomplicated cataract surgery procedure with intraocular lens (IOL) implant (see below) before inclusion in the study. The same surgical procedure was performed in the fellow eye within 3 months for all children.

The cataract extraction and IOL implant was performed in both eyes in 14 patients (DC group, 28 eyes; mean age at testing was 13.2 ± 4.1 years ranging from 5.1 to 19 years); fourteen healthy age-similar subjects served as controls (HS group, 28 eyes; mean age: 11.0 ± 4.79 years ranging from 5.1 to 18.4 years).

All patients underwent an extensive ophthalmological and orthoptic characterization. HS subjects were selected on the basis of the absence of any kind of neurological, systemic and ocular disease; HS best corrected visual acuity (BCVA) was equal to or less than −0.18 LogMAR.

At birth, all DC patients underwent an extensive ophthalmological examination, including pupillary light reflex, red reflex test, static and dynamic retinoscopy, biomicroscopy, iridocorneal angle evaluation, intraocular pressure measurement (Perkins' tonometer) and fundus examination. Each DC patient was subsequently followed every 6 months. DC patients were accurately selected among a cohort of 45 patients on the basis of the following exclusion criteria: presence of retinal, corneal or optical media disease, history of congenital glaucoma, systemic or syndromic disorders able to influence learning ability, postoperative complications including glaucoma, myopic or hyperopic refractive error greater than 3.50 diopter (spherical equivalent) and presence of any form of lens opacity before 1 year of age. Occlusion therapy was prescribed before surgery only when an interocular BCVA difference of 2 lines of ETDRS chart was present or, in preverbal age children, whether the morphology and/or the density of cataract was significantly severe in one eye.

All DC patients developed opacity later than 1 year of age (on average 3.4 ± 1.3 years) and underwent surgery on average 1.7 ± 0.8 years after the onset of the opacity (mean age at surgery was 5.1 ± 2 years).

In all DC eyes, surgical procedures consisting of mechanical anterior capsulorhexis, automated extracapsular lens extraction, posterior capsulorhexis or posterior capsulotomy and central anterior vitrectomy (performed up to 6 years of age) were performed under general anesthesia by the same experienced surgeon (A.M.). Antibiotics were postoperatively injected into the anterior chamber and dexamethasone was injected subconjunctivally after surgery [11–13]. 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 DC and from HS patients, mean age at surgery for DC patients, cataract morphology data, additional surgery and ocular motility disorders.

Each DC patient was clinically examined at several time points after surgery: two days, one week, two weeks, one month, three months, and then every six months after surgery. Occlusion therapy was prescribed post-operatively to all patients (from 2 up to 6 h as necessary). Patients interrupted occlusion therapy at the age of 12 years.

DC patients underwent electrophysiological assessment on average 8.1 ± 3.9 years after cataract removal.

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the University of Salerno. Written informed consent was obtained from all subjects, or their parents, after full explanation of the aims and modalities of the investigation.

Electrophysiological recordings

In order to investigate outer and inner retinal function, light-adapted electroretinograms (ERG) and photopic negative responses (PhNR), that reflect the function of retinal ganglion cells (RGC) [14, 15], were performed by Retimax (CSO, Firenze—Italy).

Light-adapted a- and b-wave amplitudes and implicit times and PhNR amplitudes were studied. In order to indirectly isolate photoreceptoral activity [16, 17], additional analysis of light-adapted ERG was performed by measuring a-wave amplitude at 5 ms after the light stimulus presentation.

Electrophysiological assessment was performed by using ISCEV standard protocols and skin electrodes. Technical details and procedures are described in our previously published work [11].

Test–retest results from DC 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

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

	n	Age (mean ± sd)	Age of surgery (mean ± sd)	Cataract morphology	Additional surgery	Motility disorders
HS eyes	28	11.0 ± 4.8	-	-	-	-
DC eyes	28	13.2 ± 4.1	5.1 ± 2	5 zonular 7 anterior polar 2 lamellar	2 IOL dislocation 4 Strabismus	3 Esodeviation 1 Exodeviation

HS = Healthy Subjects. DC = Developmental Cataract. IOL = intraocular lens. sd = Standard Deviation

estimated according to the methods reported by Fleiss [18] and Bland & Altman [19].

Statistics

We did apply an unpaired two-sample t-test to verify that electrophysiological data from right and left eyes of DC patients were statistically different (a-wave amplitude: $p = 0{,}61$; a-wave implicit time: $p = 0{,}58$; b-wave amplitude: $p = 0{,}71$; b-wave implicit time: $p = 0{,}61$; PhNR amplitude: $p = 0{,}89$). Therefore, data were pooled together and compared to control values (HS). A one–way analysis of variance, by using Dunnett's correction for multiple comparisons, was performed to compare ERG a- and b- wave amplitudes and implicit times, and PhNR amplitudes between groups (HS and DC eyes). For all analyses, a p-value <0.001 was considered as statistically significant. For all parameters, 95% confidence limits were obtained from age-similar normal subjects' 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 possible associations between electrophysiological parameters and BCVA data and the time elapsed from lens extraction surgery, considering as statistically significant a p-value <0.004, correcting for Bonferroni. The SAS statistical software package (version 9.1, SAS Institute Inc., Cary, NC) was used.

Results

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

Based on 95% confidence limits, the DC group showed individual abnormal values of a- and b-wave implicit time in 5/28 and 3/28 eyes, respectively, and abnormal a-, b-wave and PhNR amplitudes in 0/28, 5/28 and 5/28 eyes, respectively.

Table 2 shows mean values and relative SD of BCVA and mean light-adapted ERG a-, b- and PhNR wave amplitudes and implicit times for the two groups with the unpaired t-test results between groups.

On average BCVA values, light-adapted ERG a-, b-wave implicit times of DC eyes were significantly different when compared to HS eyes. Mean values of the DC group light-adapted ERG a- and b-wave implicit times were slightly delayed compared to the HS group (DC vs HS a-wave implicit time mean values: 17.54 vs 15.73 ms, $\Delta = +1.81$ ms; b-wave implicit time mean values: 33.27 vs 32.16 ms, $\Delta = +1.11$ ms; $p < 0.001$).

In the DC group, no significant differences were found when mean light-adapted ERG a-, b-wave and PhNR amplitudes were compared to HS group (see Table 2; $p = 0.001$, $p > 0.001$, $p > 0.001$ respectively).

In addition, Table 2 shows that DC eyes' mean amplitude values of light-adapted ERG a-wave measured at 5 ms were not significantly different from those of the HS group.

Mean BCVA values of the DC group (0.01 ± 0.13 LogMAR) might be considered substantially normal even if

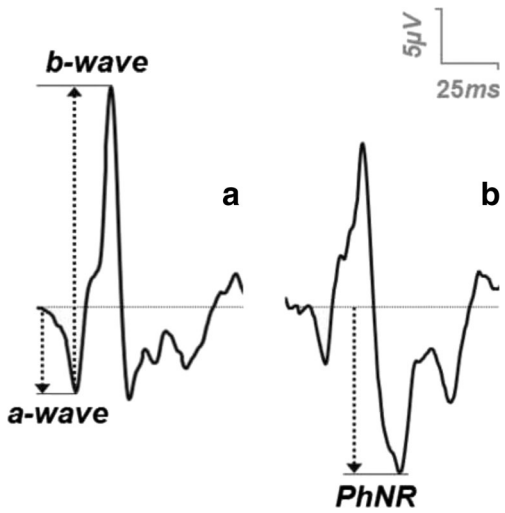

Fig. 1 Representative waveforms of the light-adapted electroretinogram (A), showing a- and b-wave amplitude (arrows) and implicit time (solid lines) values, and of the Photopic Negative Response (B) recordings from a control subject

Table 2 - Clinical and electrophysiological measurements in healthy subjects and patients with history of developmental cataract, and relative statistical analysis

	BCVA	Light-adapted ERG a-wave		Light-adapted ERG b-wave		Light-adapted ERG a-wave measured at 5 ms	PhNR
	(mean ± sd)	(mean ± sd)		(mean ± sd)		(mean ± sd)	(mean ± sd)
	LogMAR	*amplitude (μV)*	*implicit time (ms)*	*amplitude (μV)*	*implicit 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	3.96 ± 1.49	9.40 ± 2.47
DC (28 eyes)	0.01 ± 0.13	4.41 ± 1.42	17.54 ± 1.63	13.24 ± 5.21	33.27 ± 1.09	3.21 ± 1.87	7.36 ± 3.14
HS versus DC	p*	$p = 0.001$	p*	$p = 0.002$	p*	$p = 0.01$	$p = 0.02$

HS healthy subjects, *DC* developmental cataract, *BCVA* best corrected visual acuity, *ERG* electroretinogram, *PhNR* photopic negative response, *sd* standard deviation, *p** = (value <0.001) was considered as statistically significant, *LogMAR* logarithm of the minimum angle of resolution

they were significantly worse than those of the control group (−0.18 LogMAR; $p < 0.001$).

No significant correlations were found when age at surgery, time elapsed from surgery, duration of the visual deprivation, age at examination, age at first detection of the opacity, BCVA and electrophysiological parameters were plotted together.

Discussion

Although the involvement of the lateral geniculate body and cortical structures in the visual deprivation process are widely documented [20–23], the impact of visual deprivation on the retinal elements is still scarcely investigated, especially from the functional perspective. Nevertheless, this topic constitutes a growing area of interest in pediatric ophthalmology since, on the basis of the recent findings, the retinal structures are considered to have a central role in the development of visual function.

We previously proposed the congenital cataract [11], and now the developmental cataract, as two different models for examining visual deprivation effects on the cone system by using an extensive retinal electrophysiological assessment. For this purpose, light-adapted ERG and PhNR were performed for all included patients.

Our results showed a slight significant delay of implicit times of both light-adapted ERG a- and b-wave when eyes affected by developmental cataract were compared to control healthy eyes. Nevertheless, considering the small amount of delay (a-wave +1.81 ms; b-wave +1.11 ms), the light-adapted ERG may be considered, clinically, within the normal limits. In addition, although the delay of implicit times of photopic ERG components has been described in several pathological conditions such as optic nerve hypoplasia, diabetic retinopathy and retinitis pigmentosa [24–26], the functional meaning of an isolated small delay of the ERG a- and b- wave implicit times, without an association with abnormal amplitude values, is difficult to ascribe to a specific abnormal bioelectrical retinal activity. When compared to controls, DC eyes mean photopic a-, b-wave and PhNR amplitudes appeared slightly reduced and a-wave amplitudes showed borderline mean values, however, no statistically significant differences were found between the two groups ($p = 0.001$). Mean values of BCVA in DC eyes were significantly worse than control ones ($p < 0.001$).

Moreover, no significant correlations were found when age at surgery, time elapsed from surgery, lasting of the visual deprivation, age at examination, age at first detection of the opacity, BCVA and electrophysiological parameters were plotted together.

Besides BCVA values, taken together these minimal functional abnormalities of the cone retinal system are probably clinically not relevant, however, for a scientific purpose they deserve more consideration.

Structural studies of the retina

It has already been described, in animal models, that retinal organization continues far beyond birth. Indeed, it is reported that bipolar cell synapses with cones, in mice, are only completed after eye-opening [27]; the stratification of ganglion cells within the inner plexiform layer occurs in early postnatal life and involves the area centralis before peripheral retina [5]; in addition, retinal cell death, a normal process of neuronal network refinement, continues during the first weeks after birth [28]. In primates, a redistribution and differentiation of photoreceptors continues up to 5 years postnatally [6].

More recently, Hendrickson et al. described histological findings of human (postmortem) retina from gestational age to 13 years of age. They found that morphological modifications of outer retinal structures, such as cone elongation and packing, are postnatal processes extended up to adulthood; nevertheless, the refinement period of the foveal pit architecture is accomplished within 2 years of age and, although the cone packing process is not concluded, the fovea, at 3.8 years of age, is as morphologically structured as that of a 13 year-old [7, 29–31]. With the advanced usage of non-invasive imaging

techniques in pediatric ophthalmology, new interesting findings on retinal structures are now available. A recent in vivo tomographic retinal investigation described the retinal modification occurred from infancy to adult age [8]. Despite Hendrickson's histological findings [8], Lee reported that foveal outer layers increase in thickness logarithmically up to 3.8 years of age, whereas parafoveal and perifoveal outer retinal layers increase in thickness more gradually until 12 years. The inner retinal layers modify their structure up to 5.5 years of age.

Morphological studies, by using optical coherence tomography (OCT), in patients affected by congenital and acquired cataract, showed a substantially normal macular structure with increased central thickness of cataractous eyes when compared to healthy controls [31].

Neurofunctional considerations

In our recently published work [11], we described the effect of congenital cataract (defined as an opacity occurring within 6 months of birth) and consequent early light deprivation on cone driven retinal function. We reported an impairment of the entire cone-related pathway triggered, probably, from the photoreceptors' dysfunction. All components of the light-adapted ERG (a- and b-wave amplitudes and b-wave implicit time) and the amplitude of PhNR were affected in congenital cataract eyes. Our results regarding the effects of developmental cataract on cone-driven retinal function, presented in this work, describe only a slight delay of implicit times of the light-adapted ERG a- and b-waves and a normal photoreceptoral function investigated by the measurement of the a-wave amplitude at 5 ms, with a normal RGC function investigated by PhNR recording.

Taken together, all these findings lead to some neurofunctional considerations regarding the cone-related retinal pathway: 1) for the first time we describe that the function of developing cone-related retinal structures is more affected by early light deprivation (<6 months of age: congenital cataract) than by "late-onset" (>12 months of age: developmental cataract) visual deprivation; 2) the cone-related retinal function impairment, due to congenital cataract, persists after adolescence and might be considered virtually permanent; 3) consistently with the above-mentioned morphological studies by Lee and Hendrickson, the extremely light functional impairment of the photopic ERG (consisting of slight delay of a- and b-wave implicit times and borderline values of a-wave amplitude) describe minimal functional abnormalities of a well-structured retina that is not completely mature; 4) a normal RGC function is present when the visual deprivation occurs after approximately two years of age; 5) accordingly with structural data, RGC function is completely developed at approximately two years of age; 6) early and effective treatment of developmental cataract allows practitioners to achieve optimal visual outcomes.

This study presents some limitations: 1) clinical data are retrospectively collected and more accurate evaluation of cataract morphology is not available, therefore is not possible to assign a grading range to the developmental lens opacity considered in this study; 2) considering the different times of onset of the opacities, a larger cohort of patients would have been required to study the effect of visual deprivation on retinal function at different ages.

Despite these limitations, this is the first electrophysiological investigation performed in patients with history of developmental cataract.

Our present results, combined with our previous work [11], allows us to enhance the comprehension of functional developmental mechanisms of children's retina and highlight the relevance of the timely treatment of lens opacities during infancy.

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Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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