Age-Related Effects on the Spectrum of Cerebral Visual Impairment in Children With Cerebral Palsy

Jessica Galli¹,²*, Erika Loi³, Anna Molinaro², Stefano Calza⁴, Alessandra Franzoni⁵, Serena Micheletti², Andrea Rossi⁴, Francesco Semeraro⁴,⁵, Elisa Fazzi¹,² and CP Collaborative Group†

¹ Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy; ² Unit of Child Neurology and Psychiatry, ASST Spedali Civili of Brescia, Brescia, Italy; ³ Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy; ⁴ Department of Neurological and Vision Sciences, ASST Spedali Civili of Brescia, Brescia, Italy; ⁵ Eye Clinic, University of Brescia, Brescia, Italy

Background: Cerebral Visual Impairment (CVI) is a very common finding in children affected by Cerebral Palsy (CP). In this paper we studied the characteristics of CVI of a large group of children with CP and CVI, describing their neurovisual profiles according to three different age subgroups (subgroup 1: infants 6 months–2 years; subgroup 2: pre-school age 3–5 years; subgroup 3: school age ≥ 6 years).

Methods: We enrolled 180 subjects (104 males, mean age 66 ± 42.6 months; range 6–192 months) with CP and CVI for the study. We carried out a demographic and clinical data collection, neurological examination, developmental or cognitive assessment, and a video-recorded visual function assessment including an evaluation of ophthalmological characteristics, oculomotor functions, and basic visual functions. In school-aged children, we also performed an evaluation of their cognitive-visual profiles.

Results: There were signs of CVI in all the three subgroups. Subgroup 1 (62 children) and subgroup 2 (50 children) were different for fixation (p = 0.02), visual acuity (p = 0.03) and contrast sensitivity (p < 0.01), being more frequently impaired in younger children. Comparing subgroup 2 with subgroup 3 (68 children), the older children presented more frequently myopia (p = 0.02) while the younger ones esotropia (p = 0.02) and alteration in smooth pursuit (p = 0.03) and saccades (p < 0.01). Furthermore, fixation, smooth pursuit, visual acuity, contrast sensitivity and visual filed (p < 0.01) were more frequently impaired in younger children (subgroup 1) compared to the older ones. Multiple correspondence analysis (MCA) confirmed the different neurovisual profiles according to age: younger children with CP showed more signs of CVI compared to the older ones. 34 out of 68 children belonging to subgroup 3 underwent the cognitive visual evaluation; an impairment of cognitive visual skills was detected in 21 subjects.

Conclusion: Younger children with CP showed more signs of CVI compared to the older ones, likely for the physiological maturation of visual system and mechanisms of neuroplasticity. In this direction, we suggest an early neurovisual evaluation to detect any weak visual functions.

Keywords: cerebral visual impairment, cognitive-visual disorders, cerebral palsy, age, children
INTRODUCTION

Cerebral Visual Impairment (CVI) is the major non-ocular cause of pediatric visual impairment worldwide (Bauer and Merabet, 2019; Ortibus et al., 2019; Philip et al., 2020; Tinelli et al., 2020; Sakki et al., 2021) and it is operationally defined as “a verifiable visual dysfunction, which cannot be attributed to disorders of the anterior visual pathways or any potentially co-occurring ocular impairment” (Sakki et al., 2018; Bauer and Merabet, 2019). In recent years, there has been an increased effort to find a consensual definition of CVI (Kran et al., 2019; Ortibus et al., 2019; Sakki et al., 2021), and to identify a classification system based on clinical severity (Philip and Dutton, 2014; Sakki et al., 2021). Sakki et al. (2021) used cluster analysis to derive a medically based CVI classification, identifying three different profiles: (A1) selective visual perception and visuomotor deficits; (A2) more severe and broader visual perception and visuomotor deficits, and variable visual acuity; (B) unable to perform psychological testing (significant visual acuity reduction). The three subgroups showed profiles progressively more severe from Group A1 to Group B also for refractive errors, strabismus, nystagmus and the level of motor impairment with the majority of children belonging to Group B with Cerebral Palsy (CP). It is widely known that CVI is frequently observed in CP (Fazzi et al., 2007). We have found a great variety in its prevalence among studies (from 16 to 70%) according to the sources of clinical information used (for example direct observation, telephone questionnaires), to the different definition of visual impairment, to the methodological heterogeneity (for example different tests used for assessing the cognitive visual disorders), and to the visual parameters taken at clinical assessment (Ego et al., 2015; Duke et al., 2020; Philip et al., 2020; Tinelli et al., 2020).

The co-occurrence of CVI and CP is related to the fact that the lesions to motor pathways, particularly periventricular leukomalacia, are anatomically close to visual pathways (Fazzi et al., 2012; Tinelli et al., 2020).

The clinical spectrum of visual problems in children affected by CP is extremely broad, ranging from mild to severe, and including ophthalmological, ocularmotor, basic visual function, cognitive-visual disorders (CVDs) (Fazzi et al., 2007; Castelli and Fazzi, 2016; Merabet et al., 2016; Maioli et al., 2019; Baranello et al., 2020; Bennett et al., 2020). In children affected by CP, the severity of visual impairment seems to correlate with the severity of motor deficits (Dufresne et al., 2014). Fazzi et al. (2012) describe different neuro-ophthalmological profiles according to the type of CP. Children with tetraplegic CP showed the greatest visual impairment, presenting markedly reduced or not assessable visual acuity, highly impaired or absent ocularmotor functions, and high percentage of ocular abnormalities. Diplegic CP was characterized by moderately reduced visual acuity, altered contrast sensitivity, absent stereopsis, impaired ocularmotor abilities, refractive errors and CVDs while children suffered from hemiplegic CP presented slight reduced visual acuity, reduced visual field (frequently unilateral), altered stereopsis, less frequent ocularmotor involvement, and refractive errors. Tinelli et al. (2020) also suggest a relationship between brain lesion severity and visual function in children affected by CP: visual acuity, visual field, stereopsis and color perception were compromised in presence of a cortical damage, while ocularmotor functions in presence of a subcortical damage. Therefore, to date authors have focused on profiling the spectrum of CVI according to the type of CP (Fazzi et al., 2012) or to etiology, location, timing and extent of brain lesions (Guzzetta et al., 2001; Bennett et al., 2020; Tinelli et al., 2020).

Although visual functions progressively mature during the first years of life in healthy subjects (Luna et al., 2008; Lewis and Maurer, 2009; Helo et al., 2014), only few studies evaluated the visual profile in children affected by CP according to age, reporting inconsistent results. Ego et al. (2015) hypothesized a spontaneous improvement of ocularmotor functions, quantitatively assessed, in a cohort of children with CP, while Tinelli et al. (2020) found no correlation between the age of CP subjects and the Visual Total Score (Tinelli et al., 2020) obtained from the sum of ocularmotor (fixation, following, saccades, and nystagmus) and perceptual signs (acuity, binocular visual fields, stereopsis and color perception); for each item, the authors gave a score of 0 if “not compromised” or of 1 “when there is an impairment.” However, the visual dysfunctions considered in Visual Total Score can occur independently and their sum may hide potential underlying associations. Finally, literature data on visual function outcome in children with CVI caused by heterogeneous etiology (such as cerebral nervous system malformations, infections, injuries or seizures) reported an improvement of visual acuity, ranging between 32–83% (Matsuba and Jan, 2006; Handa et al., 2018) and contrast sensitivity (Watson et al., 2007).

Profiling the visual development of patients affected by CVI and CP is a crucial starting point to ameliorate their follow-up. Understanding the developmental trajectories of each impaired visual function may allow health professionals to: (1) define the type and the timing of rehabilitation, directing resources toward those functions that have till the possibility for improvement and, at the same time, preventing them from being further compromised; (2) advance the awareness and understanding of mild spectrum of CVI that can go unrecognized until it interferes with learning and daily life activities; (3) improve counseling offered to families regarding the developmental trajectories of each impaired visual function.

Our hypothesis is that the clinical spectrum of CVI can modify during the first years of life and that the youngest children can present more signs of CVI in terms of visual dysfunctions compared to the older ones. In fact, in literature we found data that attests that age-related visual development is due to maturation of brain anatomy and function (Luna et al., 2008). Moreover, visual deficits caused by early brain damage could be influenced by adaptive neuroplasticity that, especially during the first years of life, modulate the natural history of children suffering from CP and CVI (Ismail et al., 2017; Sabel et al., 2018; Fiori et al., 2019).

The aims of our study were: (1) to detail the neurovisual profile (that means ophthalmological, ocularmotor and basic visual functions) of a large group of children affected by CP according to three different age subgroups (subgroup 1: infants 6 months–2 years; subgroup 2: pre-school age 3–5 years; subgroup 3:
school age > 6 years), (2) to compare age subgroups. Finally, (3) we wanted to know whether cognitive visual functions in the oldest age group were different from reference values and whether the presence of cognitive visual disorder was related to the IQ values (FIQ, VIQ and PIQ). We divided the sample into these three age subgroups based on visual anatomical and functional aspects. Gross anatomical structures, although constructed before birth, continue to develop into adulthood, together with the maturation of neural circuits of the visual cortex (Kovács et al., 1999). Specifically, some authors suggest the hypothesis that synaptogenesis in human visual cortex reaches a peak between 8 months and 2 years and is followed by a long period of synaptic pruning to reach adult levels later in childhood (Siu and Murphy, 2018). A similar trajectory is seen in dendritic refinement, with a peak at 5 months and adult levels by 2 years (Siu and Murphy, 2018). Many anatomical features (as cortical thickness, synaptogenesis, horizontal, and interlaminar connections, for details see the review of Siu and Murphy (2018)) are already adult-like at this stage, but vision continues to mature well beyond the first years of life. In fact, lower visual functions (such as visual acuity) reach adult level between 3 and 5 years of age, while higher level visual function (such as figure-ground discrimination and visual attention) complete their development in adolescence (Dutton, 2003; Ortibus et al., 2019). However, the precise age of maturation may vary significantly depend on test design (e.g., because of potential validity issues), that in turn hinders estimations of function development and on the visual experience of the child. Finally, literature data report that the time windows of (critical) visual function development, which could increase the opportunity for effective treatment, are under 5 years of age (Siu and Murphy, 2018).

MATERIALS AND METHODS

Participants

193 children with CP were referred to our Neuro-ophthalmological Tertiary Center of Child Neurology and Psychiatry Unit, Civil Hospital of Brescia, between July 2017 and July 2020, by medical specialists, as pediatricians and child neurologists and psychiatrists, because of a visual impairment screening. Of these, 13 children (infants 6 months–2 years: 5 cases; pre-school age 3–5 years: 3 cases; school age > 6 years: 5 cases) were excluded from the study because they did not show any visual signs. The remaining 180 (104 males, 76 females) met the inclusion criteria and were selected for this study. Inclusion criteria were: diagnosis of CP, confirmed by neurological examination and brain Magnetic Resonance Imaging (MRI); age between 6 months and 18 years; presence of CVI according to Sakki et al. (2018, 2021). We made a CVI diagnosis according to the European definition “a verifiable visual dysfunction, which cannot be attributed to disorders of the anterior visual pathways or any potentially co-occurring ocular impairment.” We enrolled all the CP subjects with a variable association of: oculomotor dysfunctions (abnormalities in fixation and/or smooth pursuit and/or saccades and/or abnormal ocular movements); basic visual function deficits (reduced visual acuity and/or visual field and/or altered contrast sensitivity); CVDs and larger optic disc cupping associated with optic nerve hypoplasia due to mechanism of trans-synaptic degeneration (Jacobson et al., 1997). These visual signs were not primarily caused by disorders of the anterior visual pathways (globe, retina, or anterior optic nerve).

The sample did not include any children presenting severe visual deficits due to abnormalities of the anterior segment or sequelae of retinopathy of prematurity in order to exclude subjects affected by mainly ocular visual impairment.

The study was conducted in accordance with the ethical guidelines established by the Declaration of Helsinki and was approved by the Ethics Committee of Brescia (NP 3070). Written informed consent was obtained by all participants and/or their parents before data collection.

Procedure

A demographic and clinical data collection, a neurological examination with gross and fine motor evaluation, a developmental or cognitive assessment and a video-recorded visual function examination was carried out in the children affected by CP and CVI. Data on neuroradiological findings (Conventional Brain MRI) of all CP children were also collected. We classified CP based on criteria outlined in the Surveillance of CP in Europe algorithm Surveillance of Cerebral Palsy in Europe (2000), into four subtypes: Spastic bilateral CP, Spastic unilateral CP, Dyskinetic CP, Ataxic CP. The Gross and Fine motor function was assessed using the Gross Motor Function Classification System (GMFCS) (Palisano et al., 1997) and the Manual Ability Classification System (MACS) (Eliasson et al., 2006), respectively. To assess developmental or cognitive skills, the Griffiths Mental Developmental Scales-III (Green et al., 2017), Wechsler Preschool and Primary Scale of Intelligence III edition (WPPSI-III) (Wechsler, 2002) or the Wechsler Scales of Intelligence for Children IV edition (WISC-IV) (Wechsler, 2003) were used according to the age of the children. The developmental/intelligence quotients (IQ) were measured in standard scores and defined normal (≥ 85 standard score), mildly/moderately impaired (<85 standard score).

We carried out the visual assessment according to Fazzi and colleagues (Fazzi et al., 2012; Iodice et al., 2018) and included the evaluation of: (1) ophthalmological characteristics, detecting possible refractive errors (assessed in cycloplegia), anterior segment and ocular fundus abnormalities; dynamic retinoscopy was not carried out; (2) oculomotor functions (fixation, smooth pursuit, and saccades and orthoptic evaluation to detect strabismus, ocular motility deficit and abnormal eye movements); (3) basic visual functions (visual acuity, contrast sensitivity, visual field); (4) cognitive-visual profile, carried out in children at school-age (subgroup 3) with normal IQ or mild cognitive impairment (full-scale IQ > 50 and verbal IQ > 70 standard scores) and visual acuity not less than three-tenths in binocular vision. As regards oculomotor functions, we defined fixation as present (stable for more than 3 s) or impaired (unstable or absent); we defined smooth pursuit as present (continuous) or impaired (discontinuous or difficult to elicit/absent); we defined saccadic eye movements as present (both latency and amplitude
of saccade were normal) or impaired (dysmetric and/or with increased latency or absent). Visual acuity was evaluated under maximum refractive correction with test suitable for patient's age and cooperation using Teller Acuity Cards (Teller et al., 1986), Lea Symbols or letter optotypes (Hyvärinen et al., 1980): children belonging to subgroup 1 were evaluated using Teller Acuity Cards while children belonging to subgroup 2 and 3 using Teller Acuity Card, Lea Symbols or letter optotypes. We defined visual acuity score as normal or reduced: for children belonging to subgroup 1 we used normative data according to Teller acuity cards Handbook (Teller et al., 1986); for children belonging to subgroup 2 we applied age-specific norms according to the Current American Academy of Pediatrics guidelines updated in 2016 (Donahue et al., 2016) (normal visual acuity > 4 tenths for 36–47 months, > 5 tenths for 48–59 months and > 6 tenths for ≥ 60 months of age); for the children belonging to subgroup 3 we referred to the WHO International Classification of Disease-10 definition of visual impairment (World Health Organization [WHO], 2004) (normal vision > 8 tenths; deficient < 8 tenths). We evaluated contrast sensitivity using the Hiding Heidi Low Contrast “Face” Test (HH). Since Leat and Wegmann (2004) reported that most children aged between 1 and 8 years old correctly responded to the lowest contrast at the HH, we considered the ability to identify targets as “normal” at 1.25% contrast level and as “altered” when ≥ 2.5%. We evaluated the ability to locate targets presented in different areas of the visual field binocularly using kinetic perimetry (van Hof-van Duin et al., 1992), based on child’s behavioral reactions (e.g., movements of the head, eyes, or a limb toward the target) and we classified it as normal or reduced, according to age-specific normative data reported in the literature (Heersma et al., 1989; Wilson et al., 1991; van Hof-van Duin et al., 1992); we considered normal a result within 2 standard deviation.

We performed the cognitive-visual assessment using a battery of tests referring to visual motor and visual perceptual skills. Visual motor skills were analyzed using the Developmental Test of Visual-Motor Integration - VMI- (Beery and Buktenica, 2000), a paper-and-pencil test for visual motor integration abilities, and the Block Construction - BC- task, a subtest of NEPSY battery (Korkman et al., 2011), for constructional praxia. Visual perceptual skills, in children < 11 years old, were assessed using the Bova et al. (2007) battery that includes the evaluation of: (1) The perceptual categorization, that means the ability to recognize the structural identity of an object when its projection on the retina is altered (using the Street Completion Test (Street, 1931) - SCT-), colored photographs of objects viewed from unusual perspectives - UP-, photographs illuminated in unusual ways - UI-), (2) The constancy of internal representation of objects (using a series of Imaginary Figures - IF-), and (3) The Semantic categorization, which is the capacity of recognizing semantic and functional attributes of stimuli (using Matching Tasks respectively - MC- and - MF-). We used the Street Completion Test on children > 11 years old to evaluate visual perceptual skills. Visual motor and visual perceptual functions were considered impaired if z score derived from normal controls was under -2 on at least one of the tasks evaluated. A CVD was considered present in case of visual motor and/or visual perceptual dysfunction.

A multidisciplinary team carried out the visual function evaluation: a child neuropsychiatrist performed the oculomotor/basic visual functions assessment supported by a child therapist who conducted the video-recording; an ophthalmologist performed the ophthalmology evaluation, an orthoptist detected the presence of strabismus, ocular motility deficit and abnormal eye movements and a neuropsychologist assessed the cognitive visual functions. The video-recorded examination allows the teams to observe and judge the child performance (especially the qualitative functions as fixation, smooth pursuit and saccadic movements).

We classified Brain MRIs according to the MRI Classification System proposed by the Surveillance of Cerebral Palsy in Europe (Himmelmann et al., 2017), that consists of five main groups: (A) maldevelopments, (B) predominant white matter injury, (C) predominant gray matter injury, (D) miscellaneous, and (E) normal finding.

**Statistical Analysis**

Demographic data, clinical features (subtype of cerebral palsy, level of gross and fine motor impairment, IQ) and the neuroimaging findings of the entire sample and of the three subgroups were described using means, standard deviation, and range for quantitative variables (gestational age, birth weight) and counts and percentage for qualitative variables (subtype of cerebral palsy, level of gross and fine motor impairment, IQ and brain MRI classification). Comparison between age subgroups and these variables were performed using Kruskal-Wallis test for quantitative variables and Chi squared test for qualitative variables.

For the first aim, data on neurovisual profile according to the three different age subgroups were described using means, standard deviation, and range for quantitative variables (visual acuity and contrast sensitivity) and counts and percentage of impaired qualitative variables (ophthalmological, oculomotor functions and basic visual functions). For the second aim, we compared the evolution of neurovisual profiles between the different age subgroups using a logistic regression model for all visual variables (ophthalmological, oculomotor and basic visual functions), results were reported as odds ratio (OR) and 95% Confidence Interval (CI). We carried out a multiple correspondence analysis (MCA) to investigate the relationships between categorical variables: refractive errors, fundus oculi abnormalities, strabismus, nystagmus, fixation, smooth pursuit and saccadic alterations, abnormal visual acuity, altered contrast sensitivity and visual field deficit (visual motor and visual perceptual disorders were not included in the analysis because assessed only in the subgroup 3). The 10 visual items were dichotomized ("yes/no" when the visual disorder was present/absent). The MCA approach provides coordinate plots that can be graphically interpreted as follow: (1) variable categories with a similar profile are grouped together; (2) negatively correlated variable categories are positioned on opposite sides of the plot origin (opposed quadrants); (3) the distance between category points and the origin measures the quality of the variable category on the factor map; (4) category points that are away from the origin are well represented on the
factor map. The quality of the representation of each variable is called the squared cosine (cos²), which measures the degree of association between variable categories and a particular axis. We added age (categorized) as a supplementary variable, that is, it was not used to generate the principal dimensions but rather the category coordinates were projected on the coordinate plot defined by the active variables (10 visual items). Multiple comparisons’ p-values were adjusted using Tukey algorithm.

For the third aim, data on cognitive visual functions in the oldest age group were described using counts and percentage of the impaired visual motor and visual perceptual variables. The relationship between the presence of cognitive visual disorder and IQ values (FIQ, VIQ, and PIQ) was evaluated using logistic regression model; results were reported as OR and 95% CI.

All analyses were performed using R statistical package (version 4.0.3) assuming a significance threshold of 5%.

RESULTS

Of the 180 children selected for this study, 62 belonged to subgroup 1, 50 to subgroup 2 and 68 to subgroup 3. Table 1 summarizes the demographic data, the clinical features and the neuroimaging findings of the entire sample and of the three subgroups; these characteristics were comparable between each of the three subgroups. Data on neurovisual profiles (ophthalmological, oculomotor and basic visual functions) of the three subgroups are summarized in Table 2 and Figures 1–3.

Comparison of the Neurovisual Profiles Between the Three Subgroups

Comparing the neurovisual profiles between subgroup 1 and subgroup 2, we observed that CVI signs (refractive errors, fundus oculi abnormalities, strabismus, ocular motility deficits, nystagmus, altered smooth pursuit and saccades, and visual field deficits) did not significantly differ, except for fixation (p = 0.02), visual acuity (p = 0.03) and contrast sensitivity (p < 0.01) that were more frequently impaired in younger children (subgroup 1). From the comparison of the neurovisual profiles between subgroup 2 and subgroup 3, we found no differences in refractive errors (although myopia was more frequent, p = 0.02, and hypermetropia less frequent, p = 0.052 in the subgroup 3), fundus oculi abnormalities and nystagmus. The two subgroups

| TABLE 1 | Demographic, anamnestic, clinical, and neuroradiological characteristics of the sample and of the age subgroups. |
|----------|------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-----------------|
|          | Total sample | Subgroup 1 | Subgroup 2 | Subgroup 3 | P-value |
| N subjects | 180 | 62 | 50 | 68 | 0.576 |
| Mean age (mo) ± SD (range) | 66 ± 42 (6–192) | 21 ± 8.3 (6–35) | 58 ± 9.9 (36–71) | 111 ± 25.8 (75–192) | 0.838 |
| Male/Female distribution N (%) | 104 (58)/76 (42) | 37 (60)/25 (40) | 31 (62)/19 (38) | 36 (53)/32 (47) | 0.935 |
| Preterm birth N (%) | 105 (59.0) | 33 (53.2) | 28 (57.1) | 44 (65.7) | 0.280 |
| Mean birth weight (g) ± SD (range) | 2289 ± 968 (380–4860) | 2265 ± 936 (620–3700) | 2343 ± 1.068 (380–4630) | 2270 ± 932 (800–4860) | 0.935 |
| Type of cerebral palsy: | | | | | 0.722 |
| Spastic unilateral, N (%) | 63 (35) | 17 (27) | 18 (36) | 29 (43) | 0.613 |
| Spastic bilateral, N (%) | 94 (52) | 37 (60) | 27 (54) | 29 (43) | 0.769 |
| Dyskinetic, N (%) | 20 (11) | 8 (13) | 4 (8) | 8 (12) | 0.623 |
| Ataxic, N (%) | 3 (2) | 0 | 1 (2) | 2 (3) | 0.649 |
| Gross motor involvement: | | | | | 0.649 |
| Mild (GMFCS level 1 or 2), N (%) | 90 (50) | 28 (45) | 25 (50) | 37 (54) | 0.0623 |
| Moderate (GMFCS level 3), N (%) | 7 (4) | 2 (3) | 1 (2) | 4 (6) | 0.059 |
| Severe (GMFCS level 4 or 5), N (%) | 83 (46) | 32 (52) | 24 (48) | 27 (40) | 0.057 |
| Fine motor involvement: | | | | | 0.057 |
| Mild (MACS level 1 or 2), N (%) | 102 (57) | 32 (52) | 29 (58) | 41 (60) | 0.057 |
| Moderate (MACS level 3), N (%) | 25 (14) | 9 (14) | 7 (14) | 9 (13) | 0.057 |
| Severe (MACS level 4 or 5), N (%) | 53 (29) | 21 (34) | 14 (28) | 18 (27) | 0.057 |
| Developmental/Cognitive quotient: | | | | | 0.057 |
| Normal, N (%) | 55 (31) | 17 (27) | 18 (36) | 20 (29) | 0.057 |
| Mild/moderate impaired, N (%) | 125 (69) | 45 (73) | 32 (64) | 48 (71) | 0.057 |
| Brain MRICS: | | | | | 0.057 |
| MRICS type A, N (%) | 7 (4) | 2 (3) | 3 (6) | 2 (3) | 0.057 |
| MRICS type B, N (%) | 106 (59) | 38 (61) | 28 (56) | 40 (59) | 0.057 |
| MRICS type C, N (%) | 49 (27) | 18 (29) | 11 (22) | 20 (29) | 0.057 |
| MRICS type D, N (%) | 18 (10) | 4 (7) | 8 (16) | 6 (9) | 0.057 |

N, number; mo, months; yr, years; SD, Standard deviation; GA, gestational age; wks, weeks; g, grams; GMFCS, gross motor function classification system; MACS, manual ability classification system; MRICS, magnetic resonance imaging classification system.
TABLE 2 | Neurovisual profiles between the three subgroups.

| Subgroup 1 (N = 62) | Subgroup 2 (N = 50) | Subgroup 3 (N = 68) | Comparison between subgroups, OR (CI 95%); p-value |
|---------------------|---------------------|---------------------|--------------------------------------------------|
| Refractive errors N | 58                  | 47                  | 63                  | 1 vs. 2 1.06 (0.1; 6.2); p = 0.98; 0.80 (0.1; 4.0); p = 0.93; 0.87 (0.1; 4.0); p = 0.96 | 1 = 2 = 3 |
| Mixed refractive errors | 42                  | 35                  | 44                  | 1 vs. 2 1.1 (0.4; 2.7); p = 0.94; 0.7 (0.3; 1.8); p = 0.76; 0.8 (0.3; 1.9); p = 0.89 | 1 = 2 = 3 |
| Astigmatism (isolated/mixed) | 52                  | 41                  | 54                  | 1 vs. 2 0.88 (0.2; 2.6); p = 0.93; 0.85 (0.2; 2.4); p = 0.91; 0.74 (0.2; 2.0); p = 0.72 | 1 = 2 = 3 |
| Hypermetropia (isolated/mixed) | 37                  | 33                  | 31                  | 1 vs. 2 1.31 (0.5; 3.1); p = 0.70; 0.43 (0.1; 1.0); p = 0.002; 0.57 (0.2; 1.2); p = 0.19 | 1 = 2 > 3 |
| Myopia (isolated/mixed) | 13                  | 8                   | 25                  | 1 vs. 2 0.72 (0.2; 2.1); p = 0.71; 3.05 (1.1; 8.3); p = 0.02; 2.19 (0.9; 5.3); p = 0.09 | 1 = 2 < 3 |
| Anterior segment Ab N | 4                   | 1                   | 4                   | 1 vs. 2 0.3 (0.02; 3.6); p = 0.45; 3.06 (0.2; 35.2); p = 0.44; 0.9 (1; 4.5); p = 0.98 | 1 = 2 = 3 |
| Fundus oculi Ab N | 38                  | 30                  | 45                  | 1 vs. 2 0.95 (0.4; 2.2); p = 0.97; 1.30 (0.5; 3.0); p = 0.70; 1.24 (0.5; 2.7); p = 0.77 | 1 = 2 = 3 |
| Disc pallor | 18                  | 16                  | 27                  | 1 vs. 2 1.15 (0.4; 2.8); p = 0.9; 1.4 (0.5; 3.3); p = 0.58; 1.61 (0.7; 3.6); p = 0.34 | 1 = 2 = 3 |
| Disc cupping | 9                   | 3                   | 6                   | 1 vs. 2 0.38 (0.08; 1.7); p = 0.27; 1.52 (0.3; 7.5); p = 0.76; 0.57 (0.1; 1.9); p = 0.5 | 1 = 2 = 3 |
| Disc pallor, cupping, nerve hy | 11                  | 11                  | 12                  | 1 vs. 2 1.31 (0.4; 3.7); p = 0.78; 0.76 (0.2; 2.1); p = 0.77; 0.99 (0.3; 2.7); p = 1.00 | 1 = 2 = 3 |
| Strabismus N | 47                  | 38                  | 43                  | 1 vs. 2 1.01 (0.3; 3.7); p = 0.99; 0.54 (0.2; 1.3); p = 0.23; 0.55 (0.2; 1.3); p = 0.21 | 1 = 2 = 3 |
| Esotropia | 30                  | 26                  | 20                  | 1 vs. 2 1.16 (0.5; 2.6); p = 0.88; 0.38 (0.1; 0.9); p = 0.02; 0.44 (0.2; 1.0); p = 0.002 | 1 = 2 > 3 |
| Exotropia | 17                  | 12                  | 23                  | 1 vs. 2 0.86 (0.3; 2.2); p = 0.89; 1.45 (0.5; 3.6); p = 0.54; 1.25 (0.5; 2.9); p = 0.77 | 1 = 2 = 3 |
| EOM deficit N | 33                  | 25                  | 26                  | 1 vs. 2 0.88 (0.3; 2.0); p = 0.9; 0.62 (0.2; 1.4); p = 0.33; 0.54 (0.2; 1.2); p = 0.15 | 1 = 2 = 3 |
| Abduction deficit | 25                  | 19                  | 20                  | 1 vs. 2 0.91 (0.3; 2.1); p = 0.94; 0.66 (0.2; 1.6); p = 0.5; 0.62 (0.2; 1.4); p = 0.32 | 1 = 2 = 3 |
| Upshoot in adduction | 3                   | 2                   | 3                   | 1 vs. 2 0.82 (0.1; 6.5); p = 0.95; 1.1 (0.1; 8.6); p = 0.99; 0.91 (0.1; 5.8); p = 0.98 | 1 = 2 = 3 |
| Upshoot in abduction | 5                   | 4                   | 3                   | 1 vs. 2 0.99 (0.2; 4.6); p = 1.00; 0.53 (0.09; 3.0); p = 0.63; 0.53 (0.1; 2.8); p = 0.59 | 1 = 2 = 3 |
| Nystagmus N | 27                  | 19                  | 31                  | 1 vs. 2 0.79 (0.3; 1.8); p = 0.76; 1.37 (0.5; 3.1); p = 0.80; 1.09 (0.5; 2.3); p = 0.95 | 1 = 2 = 3 |
| Fixation Ab N | 41                  | 21                  | 27                  | 1 vs. 2 0.37 (0.1; 0.8); p = 0.9; 0.91 (0.3; 2.1); p = 0.95; 0.34 (0.2; 1.7); p = 0.01 | 1 = 2 > 3 |
| Smooth pursuit Ab N | 58                  | 45                  | 49                  | 1 vs. 2 0.62 (0.1; 2.9); p = 0.71; 0.2 (0.09; 0.9); p = 0.03; 0.1 (0.05; 0.6); p < 0.01 | 1 = 2 > 3 |
| Saccadic Ab N | 51                  | 47                  | 49                  | 1 vs. 2 3.38 (0; 7.15; 3.3); p = 0.13; 0.16 (0.04; 0.6); p = 0.003; 0.56 (0.2; 1.4); p = 0.29 | 1 = 2 > 3 |
| Visual acuity deficit | 54                  | 34                  | 35                  | 1 vs. 2 -1.1 (-2.2; -0.08); p = 0.03; -0.69 (-1.5; 0.1); p = 0.13; -1.85 (-2.8; -0.8); p < 0.01 | 1 = 2 > 3 |

N, number; Ab, abnormalities; hy, hypoplasia; EOM, extrinsic ocular motility; Lea Sy, Lea symbols, letter O, letter optotype. Bold and italic values represent significant findings.
Moreover, neurovisual profile was significantly different between subgroup 1 and 3 for fixation, smooth pursuit, visual acuity, contrast sensitivity and visual filed ($p < 0.01$) being less frequently impaired in the older children (subgroup 3). Findings are summarized in Table 2 and in Figures 4–6.

**MAC Analysis**

MCA (Figure 7) was able to explain 46% of the total variation using the two main dimensions (Supplementary Figure 1). The

![Figure 1](image1.png)

**FIGURE 1** | Ophthalmological disorders according to age subgroups. A. Segment Ab, Anterior Segment abnormalities; Fundus Oculi Ab, Fundus Oculi abnormalities.

![Figure 2](image2.png)

**FIGURE 2** | Oculomotor disorders according to age subgroups. EOM deficit, extrinsic ocular motility deficit; Ab, abnormalities; S. Pursuit, smooth pursuit.

![Figure 3](image3.png)

**FIGURE 3** | Basic visual function disorders according to age subgroups. VA deficit, visual acuity deficit; C. Sensitivity Ab, Contrast Sensitivity abnormalities; V. field deficit, visual field deficit.

significantly differed for esotropia ($p = 0.02$), and alteration of smooth pursuit ($p = 0.03$) and saccades ($p < 0.01$), more frequently present in subgroup 2.

![Figure 4](image4.png)

**FIGURE 4** | Comparison between subgroups, OR (CI 95%): ophthalmological disorders. A. Segment Ab, Anterior Segment abnormalities; Fundus Oculi Ab, Fundus Oculi abnormalities.

![Figure 5](image5.png)

**FIGURE 5** | Comparison between subgroups, OR (CI 95%): oculomotor disorders. EOM deficit, extrinsic ocular motility deficit, Ab, abnormalities; S. Pursuit, smooth pursuit.

![Figure 6](image6.png)

**FIGURE 6** | Comparison between age subgroups for refractive errors.

MCA (Figure 7) was able to explain 46% of the total variation using the two main dimensions (Supplementary Figure 1). The
A coordinate plot documented two possible average profiles. In the first, the 10 visual items were predominantly impaired, while the second was characterized by the absence of visual problems. We added age subgroups as a supplementary variable in order to address the interpretation of those profiles: the younger children (6 months – 2 years) fitted perfectly in the first profile, while the older ones (> 6 years) were consistent with the second profile. Only the presence/absence of refractive errors remained distant from the two profiles, probably because they were extremely frequent in all three age-subgroups and they seem basically unrelated to visual dysfunctions. The squared correlation of each variable to the first two MCA dimensions are provided in Figure 8.

### Cognitive-Visual Evaluation in Subgroup 3 (> 6 Years)

Thirty-four out of 68 children (50%) met the criteria for the cognitive-visual evaluation. The mean age was 112.9 months (SD 28, range 72–192 months), 17 (50%) were females and 17 males (50%). The mean gestational age was 35.5 weeks (SD 5.2, range 24–42 weeks), 14 (41%) were born preterm and 20 (59%) at term; the mean birth weight was 2,408 g (SD 921.1, range 680–3,810 g). 20 children (59%) presented a spastic unilateral CP and 14 (41%) a spastic bilateral CP; the level of gross motor impairment at GMFCS evaluation was mild in 27 cases (79%), moderate in 2 (6%) and severe in 5 subjects (15%), while the level of manual ability impairment at MACS was mild in 29 children (85%) and moderate in 5 (15%). The mean full IQ was 82.1 standard scores -s.s.- (SD 17.2, range 70–114 s.s.), the mean Verbal IQ was 93.2 s.s. (SD 14.9, range 70–139 s.s.) and the mean Performance IQ was 77.5 s.s. (SD 22, range 43–127 s.s.). Brain MRIs lesion were classified as predominant white matter injury in 22 subjects (65%), predominant gray matter injury in 10 (29%) and miscellaneous in 2 cases (6%).

30 children aged < 11 years underwent all the 8 tasks for cognitive visual assessment while 4 aged > 11 years completed
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FIGURE 8 | Squared Correlations ($r^2$) between each variable and the first two main Dimensions 1 and 2. The $r^2$-values related to the two dimensions determined by the MCA for 10 variables, identified from the neurovisual evaluation carried out in 180 children belonging to the three different age subgroups. Dimension 1 accounts for 32.6% of the variance in this analysis, while Dimension 2 accounts for 12%.

the VMI, BC and SCT. An impairment of cognitive visual skills was detected in 21 out 34 subjects (18 aged < 11 years; 62%). See Table 3 for details on impaired cognitive visual performances of the 21 children. BC, VMI, UP and UL seemed to be the most frequently impaired tasks as detailed in Figure 9. The statistical analysis performed to evaluate the impact of IQ on cognitive visual disorders, revealed positive associations between FIQ and CVDs (OR 0.92; CI 95%: 0.85, 0.97; $p = 0.008$), PIQ and CVDs

TABLE 3 | Details on cognitive visual tasks of children with a CVD (belonging to subgroup 3).

| Sbj | Age (yr, mo) | FIQ/VIQ/PIQ | VA | Visual motor tasks | Visual perceptual tasks |
|-----|-------------|-------------|----|---------------------|------------------------|
|     |             |             |    | BC                  | VMI                    | SCT | UP | UL | IF | MC | MF |
| 1   | 6           | 114/139/77  | 0.7| –2                  | –3.2                   | –1.3| –1.4| –4.9| 0  | –9.6| –6.6|
| 2   | 6,7         | 78/114/50   | 0.5| –1.6                | –3.1                   | –1.3| –1.7| –2.5| –0.7| –3.6| –0.6|
| 3   | 7.2         | 73/87/45    | 0.4| –3                   | –4                     | –1.9| –3.2| –2.1| –1.4| –1.6| –1.4|
| 4   | 7.3         | 87/98/87    | 0.5| –2.8                 | –2                     | 0.4 | –0.5| –0.8| 0.8 | 0.3 | 0.8 |
| 5   | 7.4         | 70/88/43    | 0.5| –8.1                 | –2.7                   | –3.6| –2.2| –2  | –1  | 0   | 0   |
| 6   | 7.5         | 76/81/76    | 0.9| –2.3                 | –1.5                   | 0.6 | –0.5| 0.6  | –0.6| 0   | 0   |
| 7   | 7.6         | 53/88/63    | 0.3| –6.4                 | –6.4                   | –2.7| –4.6| –7.3| –5.2| 0   | 0.7 |
| 8   | 8.1         | 85/92/82    | 1  | –2                   | –1.6                   | 0.6 | –0.2| 1.1  | 0.5 | 0   | 0.7 |
| 9   | 8.1         | 55/70/48    | 0.8| –2.6                 | –2.2                   | –0.4| –1.4| –3.9| 0.4 | 0   | –2.8|
| 10  | 8.5         | 87/99/77    | 0.9| –3                   | –2                     | –2.3| –2.5| –0.8| –1.8| 0.3 | 0.7 |
| 11  | 9           | 99/92/107   | 0.6| –0.3                 | 0.5                    | 0.4 | –1.6| –2.5| 0   | 0   | 0.7 |
| 12  | 9           | 50/70/48    | 0.9| –2.6                 | –2.7                   | –1  | –2.1| –2  | –1.2| 0   | –2.1|
| 13  | 9           | 77/92/66    | 0.9| –2                   | –1.9                   | –1.6| –2.7| –2  | –3.5| 0   | 0.4 |
| 14  | 9.5         | 75/102/52   | 1  | –3                   | –3.7                   | 0.4 | –4.8| –6.2| –2.8| –1.8| –2.8|
| 15  | 10          | 57/70/53    | 1  | –2                   | –1.8                   | –2.3| –2.5| –5.4| –5.5| 0   | 0   |
| 16  | 10.8        | 67/70/77    | 0.6| –1.3                 | –1.1                   | –0.2| –2.5| 0   | –2.4| 0   | 0   |
| 17  | 11          | 70/70/83    | 1  | –2                   | –1.7                   | 0.6 | –0.9| 0.2  | 0   | 0   | 0   |
| 18  | 11          | 70/100/56   | 1  | –2.7                 | –2.4                   | –0.8| –4.5| –3  | –10.3| 0   | 0   |
| 19  | 11.8        | 55/77/45    | 1  | –3.3                 | –2.1                   | –2.3| 0   | 0   | 0   | 0   | 0   |
| 20  | 13.6        | 97/110/93   | 1  | –1.3                 | –0.8                   | –2.8| 0   | 0   | 0   | 0   | 0   |
| 21  | 16          | 83/93/76    | 1  | –3                   | –2.7                   | –2.1| 0   | 0   | 0   | 0   | 0   |

Sbj, subject; yr, years; mo, months; FIQ, full intelligence quotient; VIQ, verbal intelligence quotient; PIQ, performance intelligence quotient; VA, visual acuity in tenths; BC, Block Construction task; VMI, Developmental Test of Visual-Motor Integration; STC, Street Completion Test; UP, colored photographs of objects viewed from unusual perspectives; UL, photographs illuminated in unusual ways; IF, Imagery Figures; MC, Matching Tasks for the ability to recognize semantic attributes of stimuli; MF, Matching Tasks for the ability to recognize functional attributes of stimuli.
to observe and judge the child performance at a later time. The video-recordings of the assessment allow the professionals to make a thorough evaluation of the child's visual function and neurological development. Furthermore, the involvement of a multidisciplinary team (comprising a child neuropsychiatrist, ophthalmologist, orthoptist, and child therapist specializing in rehabilitation and development) ensures a comprehensive approach to the child's needs.

70% of the subjects and altered saccadic movements in 89%. We suggest that these findings are related to the expression of esotropia or exotropia, which are the most common in CP children (Collins, 2014; Park et al., 2016). Several factors may be associated with hypermetropia or less frequently with myopia, especially in children with brain lesions (Sobrando et al., 1999; Saunders et al., 2010). Moreover, we observed that the high frequency of refractive errors persisted among the three age-subgroups although hypermetropia tended to decrease in contrast to the progression of myopia. These findings seem to be similar to those observed in healthy subjects. During childhood a lower percentage of hypermetropia and a higher percentage of myopia is observed due to intrinsic and extrinsic factors such as the fast progression and axial length elongation of eye as well as environment, particularly extensive near work (schooling, study, reading) that have been known to cause abnormal eye growth (Kaiti et al., 2021). The high prevalence of refractive errors in CP highlights the importance of screening for these easily treatable disorders since the first years of life. Indeed, uncorrected refractive errors can limit activities of daily living, impair the development of cognitive functions (Aghaji et al., 2013) and may increase the risk of reading difficulties (Kozeis et al., 2015).

DISCUSSION

Cerebral Visual Impairment in children with CP is researched in current literature and considered a core symptom of CP on account of its high prevalence (Dufresne et al., 2014) and its impact on daily life (Pavlova and Krägeloh-Mann, 2013). Hence, in the present study we aimed at exploring the characteristics of CVI in a large sample of children affected by CP according to three different age groups (infants 6 months–2 years; preschool age 3–5 years; school age > 6 years). Our hypothesis is that the clinical spectrum of CVI may vary according to age; particularly the older children may show a milder visual impairment characterized by a lower number of visual signs compared to the younger ones, due to visual system maturation and adaptive neuroplasticity that has implications in the organization of motor, somatosensory and visual functions (Fiori et al., 2019).

We found signs of CVI in a high percentage of children (180 out 193, 93%); this data confirms our previous study on children affected by CP (Fazzi et al., 2012) in which, for example, a reduced visual acuity was detected in 87% of the subjects and altered saccadic movements in 89%. We suggest that the higher percentage detected in the present study (compared to the one reported in literature, which ranges from 16 to 70%) is related to the evaluation method that involves a multidisciplinary team (comprising a child neuropsychiatrist, ophthalmologist, orthoptist, and child therapist specializing in visual function and neurological development). Furthermore, the video-recordings of the assessment allow the professionals to observe and judge the child performance at a later time (especially the qualitative functions as fixation, smooth pursuit and saccadic movements).

This study shows that refractive errors, especially astigmatism associated with hypermetropia or less frequently with myopia, are extremely common in children affected by CP. Our data were in line with literature (Jacobson and Dutton, 2000; Kozeis et al., 2007, 2015; Marasini et al., 2011; Fazzi et al., 2012; Park et al., 2016). It has been hypothesized that the preterm birth and postnatal distress or diseases can interfere with the normal emmetropisation process (Hsieh et al., 2012), especially in children with brain lesions (Sobrando et al., 1999; Saunders et al., 2010). Moreover, we observed that the high frequency of refractive errors persisted among the three age-subgroups although hypermetropia tended to decrease in contrast to the progression of myopia. These findings seem to be similar to those observed in healthy subjects. During childhood a lower percentage of hypermetropia and a higher percentage of myopia is observed due to intrinsic and extrinsic factors such as the fast progression and axial length elongation of eye as well as environment, particularly extensive near work (schooling, study, reading) that have been known to cause abnormal eye growth (Kaiti et al., 2021). The high prevalence of refractive errors in CP highlights the importance of screening for these easily treatable disorders since the first years of life. Indeed, uncorrected refractive errors can limit activities of daily living, impair the development of cognitive functions (Aghaji et al., 2013) and may increase the risk of reading difficulties (Kozeis et al., 2015).

Fundus oculi abnormalities were detected in more than half of children in each subgroup and no significant differences among the three groups were found. These abnormalities consist of optic disc pallor, isolated optic disc cupping and optic nerve hypoplasia and may be related to axonal loss due to brain damage (retrograde transynaptic degeneration) as reported by Jacobson et al. (1997) and in previous studies by our group (Ruberto et al., 2006; Fazzi et al., 2012).

We observed strabismus in almost three-quarters of children in each subgroup. Strabismus is common in children affected by CP (Fazzi et al., 2012) due to defects of afferent pathways caused by axonal interruption in the optic radiation (Jacobson and Dutton, 2000), abnormality of vergence neurons (Mays et al., 1986) or of the pathways involved in eye movements (Tychsen and Lisberger, 1986), maldevelopment/dysfunction of visual cortex (Tychsen et al., 1996). Esotropia was the most common type of strabismus in group 1 and 2 while exotropia in group 3. There are contrasting data on which type of ocular misalignment (esotropia vs. exotropia) is the most common in CP children (Collins, 2014; Park et al., 2016; Jeon et al., 2019; Duke et al., 2020). Several factors may be related to the expression of esotropia or exotropia, as the type and the severity of CP (Collins, 2014; Jeon et al., 2019), brain injury (Brodsky, 2016) or ethnicity (Duke et al., 2020). We hypothesized that another factor may be age, since data on healthy individuals report that exotropia occurs more frequently in infants and children at
that include many of the same brain regions involved in fixation (from subgroup 1 to subgroup 2 and from subgroup 1 to subgroup 3) according to age. Literature on physiological maturation occurring in healthy new-borns suggests that perceptual visual abilities improve with age, especially during the first years of life due to visual system maturation characterized by the development of foveal cones and refinement of retinal and cortical architecture and to environmental factors (Lewis and Maurer, 2005; Sgandurra et al., 2017; Fazzi et al., 2021). Although studies on maturation of perceptual functions in subjects with brain injury are limited, they document an improvement of these skills. In a recent study of our group (Fazzi et al., 2021) a better visual acuity and contrast sensitivity has been documented not only in infants who underwent an early visual treatment but also in the control group. We hypothesized that the developing brain would be able to “amplify” visual function through neuroplastic changes involving local and global functional connectivity networks by activating, modulating and strengthening residual visual signals (Sabel et al., 2018; Fazzi et al., 2021). As regard visual field, some authors have observed a recovery of visual field limitation in children with early brain lesions at school age, probably attributable to the maturation of the ability to shift attention rather than an enlargement of the visual field (Mercuri et al., 2003; Guzzetta et al., 2010). MCA analysis confirmed our results, underlying the differences in the expression of CVI spectrum according to age: the younger children presented a wider association of signs of visual function involvement, while the older ones had a milder CVI phenotype consisting of limited number of visual dysfunctions. Unfortunately, the cognitive visual profile could not be included in the MCA because assessed only in children over 6 years of age.

More than half of children assessed for cognitive visual functioning belonging to subgroup 3 presented signs of CVDs, with visual motor and visual perception skills often simultaneously impaired. Specifically, visual motor abilities (BC and VMI) and perceptual categorization (UP and UL) seemed to be the most affected. These difficulties seem to be related to a damage to the superior longitudinal fasciculus, connecting the occipital cortex with the parietal-frontal cortices, as documented in our previous work (Galli et al., 2018). There is no accepted prevalence of these disorders among children with CP, with the rate found to vary between 5 and 85% (Stiers et al., 2002; Fazzi et al., 2004; Atkinson and Bradlick, 2007; Pagliano et al.,
children excluded from the cognitive visual assessment will
the presence of a cognitive visual dysfunction in all the
comparison. As regards the cognitive visual evaluation, we
functions) should be judged carefully in the absence of normative
not matched; impairment rates (especially for the oculomotor
may partly be caused by group differences since they were
maturation effects
seem to improve with age in more than half of the sample
belonging to the sample presented in this work: preliminary
carrying out a longitudinal study on 50 children affected by CP
selection bias has to be considered. For this reason, we are
longitudinal design but instead selecting each subject that
we need to consider that it was not conducted using a
multidisciplinary approach that
involves the participation of several health professionals (child
examination, based on a multidisciplinary approach that
did not use questionnaires or registers to collect data,
 Instead we evaluated the children with CP directly using a
complete and detailed video-recorded visual function
examination, based on a multidisciplinary approach that
involves the participation of several health professionals (child
neuropsychiatrist, ophthalmologist, orthoptist, psychologist
and child therapists specializing in visual function and
neurological development).
Regarding potential limitations associated with the study,
 we need to consider that it was not conducted using a
longitudinal design but instead selecting each subject that
was consecutively referred to our Center. Hence, the risk of
selection bias has to be considered. For this reason, we are
 carrying out a longitudinal study on 50 children affected by CP
belonging to the sample presented in this work: preliminary
data seem to confirm our findings (oculomotor functions
seem to improve with age in more than half of the sample
while basic visual functions in about one third of cases).
Moreover, the cross-sectional design without normal controls
should also be mentioned as limitation. Maturation effects
may partly be caused by group differences since they were
not matched; impairment rates (especially for the oculomotor
functions) should be judged carefully in the absence of normative
comparison. As regards the cognitive visual evaluation,
we would mention two limitation. First, we could not investigate
the presence of a cognitive visual dysfunction in all the
children belonging to subgroup 3 due to the nature of the
tests used for the assessment; it is highly likely that the
children excluded from the cognitive visual assessment will
have had significant cognitive visual deficits (with or without
deficits in primary visual functions). Second, we cannot analyze
the effect of age on CVDs since we were able to conduct this
assessment only in those children over 6 years of age;
 further studies on characteristic of CVDs from pre-school
age to adolescence should be performed considering also a
larger sample size. Due to limited number of children assessed
for the cognitive visual performances, the interpretation of
our results needs attention and we cannot generalize them
to all the sample.
On the basis of these observations, we can conclude that
younger children with CP showed more signs of CVI compared
to the older ones. In this direction, we suggest an early
neurovisual evaluation for all these measures because it allows
to define the type of habilitative intervention, directing resources
toward the weak functions that can still improve. Acting as
early as possible is fundamental given that neuroplasticity is
maximal within the first 2 years of age (Yin et al., 2019).
In our recent work we found that, although the presence of
a spontaneous recovery, an early intervention could amplify
the visual functions and the developmental outcomes (Fazzi
et al., 2021), especially if the exposure to the visual training
happens within the first years of life (for details on visual
training please see Fazzi et al. (2021)). Moreover, an early
assessment may prevent the mild spectrum of CVI from being
unrecognized until it impacts on child's learning, mobility,
development, independence and quality of life, especially at
school age (Bauer and Merabet, 2019).
We hypothesized that the improvement of visual functions
could be related to the physiological maturation of the
visual system and mechanisms of neuroplasticity that have
induced the re-organization of visual functions after the
damage (Ego et al., 2015). However, in contrast to the
 case of ocular blindness, literature data on morphological,
structural and functional connectivity changes in subjects
with CVI have been scant because highly heterogeneity
across individuals in terms of location, timing, extent
and cause of damage (Bennett et al., 2020). There is
the need for further functional neuroimaging studies
to investigate neural correlates associate with CVI and
to the potential neuroplastic compensatory processes
(Bennett et al., 2020).

DATA AVAILABILITY STATEMENT
The original contributions presented in the study are included
in the article/Supplementary Material, further inquiries can be
directed to the corresponding author/s.

ETHICS STATEMENT
The studies involving human participants were reviewed and
approved by the Comitato Etico di Brescia, ASST Spedali Civili
di Brescia, Italy. Written informed consent to participate in this
study was provided by the participants' legal guardian/next of kin.
AUTHOR CONTRIBUTIONS
JG, EL, and AM drafted the manuscript. AM, AR, AF, and SM collected the data. SC performed the statistical analysis. JG, EF, and FS designed the study. All authors contributed to the article, reviewed the manuscript, and approved the submitted version.

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SUPPLEMENTARY MATERIAL
The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2022.750464/full#supplementary-material

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