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Optic nerve morphology as marker for disease severity in cerebral palsy of perinatal origin

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ABSTRACT

Background: It is difficult to predict the neurologic outcome and ambulatory status in children with perinatal neurologic insult until 2–5 years age. This study aims to correlate clinical optic nerve head (ONH) findings-cupping, pallor and hypoplasia, with gestational period and neurologic (motor) outcomes in patients with cerebral palsy (CP) from perinatal insults.

Methods: 54 consecutive patients with CP from perinatal insults were enrolled. Patients with intraocular disease, retinopathy of prematurity and hydrocephalus were excluded. ONH was labeled as pale, hypoplastic or large cup (cup/disc ratio ≥ 0.5) if 2 ophthalmologists independently agreed after an ophthalmoscopic examination. Inter-rater reliability was excellent.

Results: Mean age at examination was 10.98 ± 6.49 years; mean gestational period was 33.26 ± 4.78 weeks. Abnormal ONH (pallor, cupping or hypoplasia) was seen in 38/54 (70%) patients. Of patients with pallor (n = 17), 88% were quadriplegic and 82% non-ambulatory. Mean cup/disc ratio was 0.45 ± 0.22; 50% patients had large cup. Multivariate logistic regression models showed that disc pallor was associated with non-ambulatory status (OR: 21.7; p = 0.003) and quadriplegia (OR: 12.8; p = 0.03). Large cup was associated with age at examination (OR 1.15; p = 0.03). Cup/disc ratio showed positive correlation with age at examination (Pearson's r = 0.39; p = 0.003). There was no significant association of ONH parameters with gestational age.

Conclusion: Clinically observed ONH changes (pallor, cupping and hypoplasia) are common in CP. Presence of ONH pallor serves as an indicator for poor motor outcome in patients who develop CP from perinatal causes and should prompt early referral for rehabilitation.

1. Introduction

Cerebral palsy (CP) is defined as non-progressive (motor) deficits resulting from prenatal, perinatal or immediate post-natal neurologic insults [1]. Periventricular leukomalacia (PVL) is a pathologic and radiologic hallmark for premature children with CP [2]. Damage to the descending motor fibers and optic radiations in the periventricular white matter leads to motor and visual deficits. Ophthalmic manifestations in CP include refractive error, strabismus, nystagmus, decreased visual acuity, visual field defects, abnormal visual perception, eye movement difficulties and optic atrophy [3–9]. A definitive diagnosis of CP is difficult until 2–5 years of age because the neurologic deficits evolve or resolve as the brain matures and sometimes become apparent at a later age [10,11]. There is a need for a clinical non-invasive biomarker to help pediatricians and neurologists prognosticate the outcome from neurologic insult in children at high risk for developing CP. Such biomarkers could result in earlier referral to rehabilitation services. The optic nerve, which may be considered analogous to cerebral white matter tracts, can be the source of such biomarkers. Examination of the optic nerve head (ONH) by ophthalmoscopy, is a useful bedside clinical procedure that does not require sedation and has been studied in children with CP.

There are conflicting reports of an association between ONH appearance and period of gestation. In a study of 35 children with PVL,

Abbreviations: CP, cerebral palsy; ONH, optic nerve head; PVL, periventricular leukomalacia; MRI, magnetic resonance imaging; ROP, retinopathy of prematurity.

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Jacobson et al. found that neurologic insult prior to 28 weeks of gestation resulted in ONH hypoplasia, while cupping was seen when the insult occurred after 28 weeks of gestation [12]. McLoone et al. reported ONH hypoplasia in patients with grade 4 intraventricular hemorrhage but did not find a correlation between cupping and timing of perinatal insult [13]. Neither study examined the association of the severity of clinical neurologic deficits and ONH morphology. The objective of our study is to explore the relationship between ONH appearance, period of gestation, and severity of neurologic damage in a cohort of children with CP resulting from perinatal complications.

2. Methodology

This is a cross-sectional, observational study to test the hypothesis that ONH appearance in children with CP is dependent on period of gestation and severity of neurologic insult. The study protocol and consent procedures were approved by the University of Mississippi Medical Center Institutional Review Board (IRB). Eligible subjects included all children with CP resulting from perinatal complications after a benign antenatal course. Exclusion criteria included inability to obtain consent by parents or assent by the child, media opacities preventing visualization of the ocular fundus, inability of the child to participate in the ocular examination; a previous diagnosis of glaucoma; a history of intraocular inflammatory diseases, intraocular surgery or retinopathy of prematurity (ROP); history of hydrocephalus, elevated intracranial pressure or papilledema, determination by the neurologist of "progressive" condition or if CP was from other causes such as malformations. A convenience sample of 60 consecutive CP subjects who met the eligibility criteria were enrolled from the pediatric neurology clinic. Six patients were excluded from study after screening due to ROP (2), non-perinatal lesions on imaging studies and records (2), and inability to participate in funduscopic examination (2). Informed consent was obtained from the parent/guardian and verbal assent was obtained from all subjects enrolled. Table 1 describes the clinical characteristics of the subjects included in the study.

The pediatric neurologist (VV) determined eligibility by confirming the diagnosis and etiology of CP. Birth and perinatal history were reviewed for period of gestation, causes of perinatal complications and postnatal complications such as hydrocephalus and ROP. We assumed that neurologic insult in these children with a normal antenatal course occurred at the time of birth. All subjects underwent a neurologic examination by the pediatric neurologist to determine type of CP and ambulatory status. Based on motor deficits, patients were classified as quadriplegic, hemiplegic, diplegic or others (ataxic, dystonic). Ambulatory status was classified as non-ambulatory, ambulatory with assistance (use of cane, crutches or walker) or fully ambulatory (without assistive devices listed above). Available neuro-imaging studies (CT head and/or MR brain) were reviewed for the presence of periventricular white matter changes (periventricular leukomalacia) and ventricular enlargement (ventriculomegaly).

Table 1
Baseline characteristics of the cohort.

Characteristic	
Age at examination (n = 54)	Mean: 10.98 (SD 6.49) years; range 1–29 years
Period of gestation (n = 54)	Mean: 33.26 (SD 4.78) weeks; range: 24–42 weeks
Gestational age (n = 54)	Extremely preterm (<28 weeks): 16 Preterm (28–38 weeks) = 20 Term (38–42) = 16 Post-term (≥42) = 2
Presumed cause of insult (n = 54)	Preterm labor: 11 Hypertension (including eclampsia): 8 Placental and cord insufficiency: 6 Utero-cervical causes: 5 Others (including multiple causes): 24
Type of cerebral palsy (n = 54)	Hemiplegia: 12 (22.2%) Diplegia: 12 (22.2%) Quadriplegia: 27 (50%) Others: 3 (5.6%); 2 dystonia, 1 ataxia
Ambulatory status (n = 54)	Ambulatory: 23 (42.6%) Ambulatory with assistance: 9 (16.7%) Non-ambulatory: 22 (40.7%)
Radiological features n = 30 (25 MR head; 5 CT head)	Periventricular white matter lesion: 28 (93%) Ventricular enlargement: 21 (70%)

SD: Standard deviation.
MR: Magnetic resonance.
CT: Computed tomography.

After pupillary dilation, ophthalmoscopic examination was performed independently by two masked examiners who were fellowship trained in pediatric ophthalmology (SK), neuro-ophthalmology (SK) and pediatric glaucoma (DG) and thus have expertise in determining ONH morphology in children. All patients underwent ophthalmoscopic examination with an indirect and direct ophthalmoscope. The ophthalmoscopic parameters recorded included ONH color, size and cup disc ratio. Color was recorded as pink or pale after examining the ONH using a fully charged direct ophthalmoscope at 50% illumination. The presence of morphologic hypoplasia was determined clinically by finding a small nerve with abnormal branching vasculature and a horizontal disc-macula to disc-diameter ratio > 3 on indirect ophthalmoscopy [14]. Cup to disc ratio was determined clinically using the direct ophthalmoscope to evaluate the size of optic cup as a fraction of the optic disc. The margins of the optic cup are determined by following the blood vessel emerging from the optic disc until a dip was observed as the vessel emerges from the cup. Enlargement of the cup in either the vertical or horizontal dimensions was defined when the cup disc ratio was ≥0.5.

Both examiners had to independently label the cup/disc ratio ≥ 0.5 for the eye to be classified as "enlarged cup". Both examiners had to independently label the disc as pale for the eye to be classified as "disc pallor". Both examiners had to independently label the disc as hypoplastic for the eye to be classified as "hypoplastic". If either eye was classified as "enlarged cup", "hypoplastic" or "disc pallor", that subject was classified as having an enlarged cup, disc hypoplasia and disc pallor respectively. All subjects with enlarged cup to disc ratio were sent to pediatric ophthalmology for intraocular pressure measurement. Seventeen patients were evaluated by either ophthalmology or optometry and were documented to have normal intraocular pressures (<22 mmHg). Two of these had previously been labelled "glaucoma suspects" based on "enlarged cups" but had normal pressures during the examinations under anesthesia and were not treated with glaucoma medications.

2.1. Statistical analysis

Statistical analysis was performed using the SPSS 22 (IBM SPSS Statistics, Armonk, NY) and Statistical Analysis System version 9.3 (SAS Institute Inc. Cary, NC, USA). Inter-rater reliability between the two raters for ONH cupping and pallor was evaluated using Kappa's statistic for dichotomous measurements and intra-class correlation for continuous measurements. For comparison between groups we used chi-square test or Fisher's exact test for categorical variables and two sample *t*-test for continuous variables. Odds ratios of abnormal ONH morphology (pallor, cupping and/or hypoplasia) were calculated by using multivariate logistic regression adjusted for age at examination, period of gestation, type of cerebral palsy and ambulatory status. Analysis of covariance (ANCOVA) was used to evaluate the association between the average cup to disc ratio and age at examination, type of cerebral palsy, ambulatory status and period of gestation. Probability values <0.05 were considered statistically significant.

3. Results

3.1. Inter-rater reliability

Inter-rater reliability for ophthalmoscopic examination between the two examiners were excellent for ONH pallor and cup/disc ratio and