Neurodevelopment of Infants with and without Craniofacial Microsomia

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Objectives To determine whether infant cases with craniofacial microsomia (CFM) evidence poorer neurodevelopmental status than demographically similar infants without craniofacial diagnoses ("controls"), and to examine cases' neurodevelopmental outcomes by facial phenotype and hearing status.

Study design Multicenter, observational study of 108 cases and 84 controls aged 12-24 months. Participants were assessed by the Bayley Scales of Infant and Toddler Development-Third Edition and the Preschool Language Scales-Fifth Edition (PLS-5). Facial features were classified with the Phenotypic Assessment Tool for Craniofacial Microsomia.

Results After adjustment for demographic variables, there was little difference in Bayley Scales of Infant and Toddler Development-Third Edition or Preschool Language Scales-Fifth Edition outcomes between cases and controls. Estimates of mean differences ranged from –0.23 to 1.79 corresponding to standardized effect sizes of –.02 to 0.12 (*P* values from .30 to .88). Outcomes were better among females and those with higher socioeconomic status. Among cases, facial phenotype and hearing status showed little to no association with outcomes. Analysis of individual test scores indicated that 21% of cases and 16% of controls were developmentally delayed (OR 0.68, 95% CI 0.29-1.61).

Conclusions Although learning problems have been observed in older children with CFM, we found no evidence of developmental or language delay among infants. Variation in outcomes across prior studies may reflect differences in ascertainment methods and CFM diagnostic criteria. *(J Pediatr 2018;■■:■■-■■).*

Craniofacial microsomia (CFM), also known as hemifacial microsomia, is a complex congenital condition typically involving underdevelopment of the mandible and ear.[1,2] CFM occurs in approximately 1 in 3500-5600 live births,[3] with higher prevalence among Hispanic and Native American families.[4,5] CFM has been characterized as a spectrum of phenotypic anomalies ranging from isolated unilateral microtia to bilateral malformations of the ear, mandible, facial soft tissue, and orbit.[2] Other cranial and extracranial malformations may co-occur (eg, lateral oral clefts, vertebral anomalies, cardiac defects).

Among the several functional problems associated with CFM,[2] neurodevelopmental delays are perhaps the least understood and most difficult to recognize clinically. Although such deficits can strongly affect children's quality of life,[6,7] their impact can be mitigated by early evaluation and intervention.[8,9] The few existing studies of neurodevelopment in the CFM population, mostly involving older children, have suggested that severe intellectual disability is rare, but mild to moderate neurodevelopmental delays and learning problems may occur at higher rates than those found in the general population.[10-13] Given the heterogeneity of the CFM phenotype,[2] and the theorized embryologic mechanisms underlying the development of face and brain,[14] it is possible that neurodevelopmental outcomes may vary in relation to the severity and pattern of anomalies observed in this condition (eg, microtia with or without microphthalmia or vertebral defects). Although previous investigations have examined neurodevelopmental outcomes by 1 or more selected features (eg, presence or absence of extracranial anomalies),[10,11] a consistent pattern of association between phenotype and developmental outcomes has yet to emerge.

Based on the findings from previous neurodevelopmental studies, we hypothesized that infants with CFM would show lower test scores on average and a higher frequency of developmental delay than controls. In secondary analyses, we

Bayley-III	Bayley Scales of Infant and Toddler Development-Third Edition
CFM	Craniofacial macrosomia
CHLA	Children's Hospital of Los Angeles
CLOCK	Craniofacial Microsomia: Longitudinal Outcomes in Children Pre-Kindergarten
PLS-5	Preschool Language Scale-Fifth Edition
PTA	Pure tone average
SES	Socioeconomic status

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examined neurodevelopmental outcomes by (1) facial phenotype using a modified version of the pictorial Orbit, Mandible, Ear, Nerve, and Soft tissue scoring system, which includes ratings for orbital asymmetry, mandibular hypoplasia, ear anomalies, facial nerve involvement, and soft-tissue deficiency[15,16] and (2) the presence and severity of hearing impairment. We also estimated the effects of relevant covariates on neurodevelopmental status, including sex, socioeconomic status (SES), ethnicity, and bilingual home environment.

Methods

Infants between the ages of 12 and 24 months were recruited to participate in an ongoing observational, longitudinal, multicenter project called Craniofacial Microsomia: Longitudinal Outcomes in Children Pre-Kindergarten (CLOCK), which tracks the neurodevelopmental, speech and hearing outcomes, and phenotypic features of infants with and without CFM ("cases" and "controls," respectively). Participants were enrolled between 2012 and 2017 from one of 6 craniofacial centers: Children's Hospital of Los Angeles (CHLA), Children's Hospital of Philadelphia, Seattle Children's Hospital, University of Illinois-Chicago, (including Shriners Hospital for Children, Chicago), and University of North Carolina at Chapel Hill. This research was approved by the institutional review boards at all participating centers. All parents gave informed consent for their infant to participate in the study.

Cases were recruited from each site's hospital-based craniofacial centers, hospital-based clinics seeing infants or young children with CFM (eg hearing screening programs, ear, nose and throat programs), and research study websites (eg, https://www.clinicaltrials.gov). To be eligible, cases had to have (1) at least 1 of the CFM inclusion criteria developed by the Facial Asymmetry Collaborative for Interdisciplinary Analysis and Learning network (**Figure 1**; available at www.jpeds.com); (2) an age between 12 and 24 months (corrected for prematurity, when applicable, for children born between 34 and 36 weeks of gestational age); and (3) a legal guardian who was able to provide informed written consent and be willing to participate for the duration of the study. Exclusion criteria for cases included (1) diagnosis of a known syndrome (eg, Townes-Brocks, Treacher Collins, branchio-oto-renal, or Nager syndromes); (2) presence of an abnormal karyotype or major medical or neurologic conditions (eg, cancer, cerebral palsy); (3) premature birth (less than 34 weeks of gestation); (4) any circumstance that would preclude the family's ability to participate fully in the research; (5) a sibling already participating in the CLOCK study, or (6) a consenting parent who did not speak English or Spanish. Of the 219 potentially eligible cases that were approached, 108 (49%) were enrolled. Most nonparticipating families declined passively by not responding to study invitations.

We identified eligible participants with demographic characteristics that met our frequency-matching criteria for the case cohort; these included infant age and sex, family SES, and language spoken in the home (English or Spanish). Exclusion criteria for controls included (1) meeting 1 or more of the exclusionary criteria for cases; and (2) diagnosis or history of any disorder, condition, or injury that would affect facial features (eg, craniofacial malformation or deformation; facial surgery or trauma). Of the 148 potentially eligible controls who were approached, 84 (57%) were enrolled.

Measures

We used the Bayley Scales of Infant and Toddler Development-Third Edition (Bayley-III) to assess cognitive and motor skills.[17] The Bayley-III yields composite scores for both cognition and motor ability and subscale scores for fine and gross motor development. Raw scores are converted to norm-referenced standard scores (mean = 100, SD = 15) for composite scales and scaled scores (mean = 10, SD = 3) for the motor subscales. The Preschool Language Scale-Fifth Edition (PLS-5) was used to assess expressive and receptive language, using either the English or Spanish version of this norm-referenced, validated test.[18] We selected the PLS-5 over the Bayley-III language scales as the latter are available only in English, and the Spanish version of the PLS-5 includes culturally relevant items with norms from a large sample of monolingual and bilingual Spanish-speaking children.[19] The PLS-5 yields 2 scale scores, auditory comprehension and expressive communication, as well as a total language score, all based on a combination of child performance, examiner observations, and caregiver reports.

For both tests, gestational age was calculated using family report of due date and birth date. We corrected Bayley-III scores for prematurity for children born between 34 and 36 weeks of gestation. Testing was completed in English (69%), Spanish (13%), or a combination of English and Spanish (18%) determined by families' reports of their language use across settings, as well as examiners' observations of participants' language use during the study visit. Trained bilingual psychometrists used verbal Bayley-III prompts that were translated into Spanish for consistent use across sites. The PLS-5 has standardized versions in both English and Spanish. All assessments were videotaped and about 20% were double-scored for reliability by 3 of the authors. Average level of agreement for item-by-item scoring was 97%, with agreement levels for single test administrations ranging from 70% to 100%.

Cases' hearing status was based primarily on audiological information obtained as part of routine clinical care. Ninety one (84%) of cases had such data available for review. Infants with audiology data were considered to have hearing loss when they demonstrated a greater than 20 decibel pure tone average (PTA) over 4 frequencies (500, 1000, 20000, 4000 Hz; PTAs were calculated if at least 3 frequencies were present). For those cases without audiograms, hearing status was based on the absence of the external ear canal (ie, aural atresia) or external ear canal stenosis, both of which result in conductive hearing loss. In a prior investigation, 98% of children with aural atresia or external ear canal stenosis had PTA of >20 dB hearing loss.[20] This allowed us to create the following categories of hearing status for all cases: (1) "no hearing loss" was defined as the absence of atresia and a negative audiometric finding; (2) "unilateral hearing loss" referred to single-sided hearing loss based on au-

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