Developmental Correlates of Head Circumference at Birth and Two Years in a Cohort of Extremely Low Gestational Age Newborns

Karl C. K. Kuban, MD, SMEpi, Elizabeth N. Allred, MS, T. Michael O'Shea, MD, MPH, Nigel Paneth, MD, MPH, Sjirk Westra, MD, Cindy Miller, MD, N. Paul Rosman, MD, and Alan Leviton, MD

Objectives To evaluate the developmental correlates of microcephaly evident at birth and at 2 years in a cohort born at extremely low gestational age.

Methods We assessed development and motor function at 2 years of 958 children born before the 28th week of gestation, comparing those who had microcephaly at birth or 2 years with children with normal head circumference while considering the contribution of neonatal cranial ultrasound lesions.

Results A total of 11% of infants in our sample had microcephaly at 2 years. Microcephaly at 2 years, but not at birth, predicts severe motor and cognitive impairments at 2 years. A total of 71% of children with congenital microcephaly had a normal head circumference at 2 years and had neurodevelopmental outcomes comparable with those with normal head circumference at birth and 2 years. Among children with microcephaly at 2 years, more than half had a Mental Developmental Index <70, and nearly a third had cerebral palsy. The risks were increased if the child also had cerebral white matter damage on a cranial ultrasound scan obtained 2 years previously.

Conclusion Among extremely low gestational age newborns, microcephaly at 2 years, but not at birth, is associated with motor and cognitive impairment at age 2. *(J Pediatr 2009;155:344-9)*.

A head circumference more than 2 standard deviations (SD) below the mean for age defines microcephaly, an indicator of reduced brain volume,[1] and a correlate of cognitive and motor dysfunctions.[2-5] Compared with infants born at term, low birth weight and extremely low gestational age newborns (ELGANs) are at increased risk of having microcephaly at birth (congenital microcephaly), as well as subnormal head size evident later in childhood.[2,3,6] This increased prevalence of microcephaly in childhood has been attributed to brain damage or diminished brain growth associated with extreme prematurity.[2,3,6,7]

Studies of the correlates of microcephaly in preterm infants have evaluated samples defined by birth weight and not gestational age[8] or were based on small samples.[9,10] The ELGAN Study is the largest prospective epidemiologic study of infants born before the 28th week of gestation, a group that is at high risk of developmental dysfunction. Of the more than 1000 children evaluated at 24 months corrected age, 20% screened positive for autism spectrum disorder with the Modified Checklist for Autism in Toddlers (M-CHAT) screening tool,[11] greater than 40% scored below 70 on either the Mental Developmental Index (MDI) or Psychomotor Developmental Index (PDI) of the Bayley Scales of Infant Development (BSID),[12] and 12% had cerebral palsy (CP).[12] Because a head circumference more than 2 SD below the expected mean occurred at more than twice the rate expected, this sample provided an opportunity to assess the relationship between a small head and developmental dysfunction in a high-risk sample.

Methods

The ELGAN study was designed to identify characteristics and exposures that increase the risk of structural and functional neurologic disorders in ELGANs. During the years 2002–2004, women delivering before 28 weeks gestation at 14

CP	Cerebral palsy
ELGAN	Extremely low gestational age
GMFCS	Gross Motor Functional Classification Scale
HL	Hypoechoic lesions
HUS	Head ultrasound
M-CHAT	Modified Checklist for Autism in Toddlers
MDI	Mental Developmental Index
PDI	Psychomotor Developmental Index
VM	Ventriculomegaly

From the Division of Pediatric Neurology, Department of Pediatrics, Boston Medical Center, Boston University (K.K., N.R.), the Department of Biostatistics, Harvard School of Public Health (E.A.), the Neuroepidemiology Unit, Department of Neurology, Children's Hospital Boston (E.A., A.L.), Harvard Medical School (S.W.), Harvard University, and Massachusetts General Hospital (S.W.), Boston, MA, the Department of Pediatrics, Wake Forest University (T.O.), Winston-Salem, NC, the Michigan State University-Sparrow Medical Center, East Lansing, MI (N.P.); and the Yale-New Haven Hospital and Yale University School of Medicine, New Haven, CT (C.M.). All of the authors are members of the ELGAN Study Group

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participating institutions in 11 cities in 5 states were asked to enroll in the study. The enrollment and consent processes were approved by the individual institutional review boards.

Mothers were approached for consent either on antenatal admission or shortly after delivery, depending on clinical circumstance and institutional preference. A total of 1200 of the 1506 enrolled infants survived to 24 months corrected age. Forty-eight children did not undergo a neurologic examination or motor assessment, and another 163 did not undergo a developmental assessment or M-CHAT screening. An additional 31 children lacked either a birth or 2-year head circumference measure. This report is limited to the remaining 958 children.

Newborn Variables

The gestational age estimates were based on a hierarchy of the quality of available information. Most desirable were estimates based on the dates of embryo retrieval or intrauterine insemination or fetal ultrasonography before the 14th week (62%). When these were not available, reliance was placed sequentially on fetal ultrasound scanning at 14 or more weeks (29%), last menstrual period without fetal ultrasound scanning (7%), and gestational age recorded in the log of the neonatal intensive care unit (1%). For each birth weight, we calculated a Z-score, which represents the number of SD the infant's birth weight is above or below the median weight of infants, at the same gestational age in a standard data set.[13]

Head Circumference

The head circumference was measured at birth and at 24 months post-term equivalent as the largest occipital-frontal circumference. Measurements were rounded to the closest 0.1 cm. All neurologic examiners were required to view a training CD-ROM and then pass a test presented on CD-ROM, which included a section on the proper method for an accurate head circumference measurement.[14] All head circumferences were presented as Z-scores because newborns were assessed at different gestational ages at birth (23 to 27 weeks) and with different approximations of 24 months corrected age (range 16 to 44 months corrected age, with 68% assessed at 23 to 25 months corrected age). For head circumference at birth, Z scores were based on standards in the Oxford UK data set.[13] For head circumference at 24 months, Z scores were based on standards in the CDC data sets.[15] Microcephaly is defined as a head circumference Z-score less than −2 (ie, more than 2 SD below the external mean).

Protocol Scans

Routine head ultrasound scans were obtained by technicians at all of the hospitals with digitized high-frequency transducers (7.5 and 10 MHz). These studies included 6 standard coronal views and 5 standard sagittal views with the anterior fontanel used as the sonographic window.

Of the 1506 infants enrolled, 1455 had at least 1 protocol ultrasound scan set, and, of these, 1053 were examined at 2 years corrected age. The 3 sets of protocol scans were defined by the postnatal day on which they were obtained. Protocol 1 scans were obtained between the first and fourth day (n = 795); protocol 2 scans were obtained between the fifth and fourteenth day (n = 981), and protocol 3 scans were obtained between the fifteenth day and the 40th week (n = 1016). A total of 722 had all 3 sets of ultrasound studies.

Reading Procedures

After creation of a manual and data collection form, observer variability minimization efforts included conference calls, discussing any aspects of images prone to different interpretations.[16] Templates of multiple levels of ventriculomegaly were included in the manual.[17]

All head ultrasound scans (HUS) were read by 2 independent readers who were not provided clinical information. Each set of scans was first read by 1 study sonologist at the institution of the infant's birth. The images, usually as electronic images on a CD imbedded in the software eFilm Workstation (Merge Healthcare/Merge eMed, Milwaukee, Wisconsin), were sent to a sonologist at another ELGAN study institution for a second reading. The eFilm program allowed the second reader to adjust and enhance the studies similar to the original reader, including the ability to zoom and alter gains.

When the 2 readers differed in their recognition of intraventricular hemorrhage, moderate/severe ventriculomegaly (VM), and hypoechoic lesions (HL), the films were sent to a third (tie-breaking) reader (40% of the subjects), who did not know what the first 2 readers reported.

24-Month Developmental Assessment

Families were invited to bring their child for a developmental assessment close to the 24-months corrected age. Ninety-one percent of children had this developmental assessment, which included a neurologic examination and an assessment with the Bayley Scales of Infant Development, Second edition. Additionally, the parent or caregiver accompanying the child was asked to complete the M-CHAT.[18]

CP

Those who performed the neurologic examinations first studied an examination operations manual, a data collection form, and an instructional CD to minimize examiner variability.[14] The topographic diagnosis of CP (quadriparesis, diparesis, or hemiparesis) was based on an algorithm with these data.[12] Ninety-six percent of examiners indicated at the time of the examination that they had no knowledge of the child's brain-imaging studies.

Gross Motor Functional Classification Scale

The examiners were asked to rate the child on the Gross Motor Functional Classification Scale (GMFCS), separate from the neurologic examination. A level <1 indicates that the child can walk independently. A level of 2+ indicates that the child cannot walk even when the hand is held.[19]

Bayley Scales of Infant Development–Second Edition

Certified examiners administered and scored the Bayley Scales of Infant Development–Second Edition (BSID-II).