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

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Abstract

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.

Ahead 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

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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 age⁸ 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 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 intra-ventricular hemorrhage, moderate/severe ventriculomegaly (VM), and hypochoic 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 (quadriplegia, diplegia, or hemiplegia) 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). Ninety-eight percent of examiners indicated at the time of the examination that they had no more than a limited amount of information about the child. Before testing, examiners were told the child's age. After completion of testing they were told the child's gestational age so that the adjusted MDI and PDI could be calculated.

The child was classified as nontestable on a scale if her/his impairments prohibited standardized administration or if more than 2 items were judged to be “not applicable.” On the basis of their score on scale 5 of the Vineland Adaptive Behavior Scales, 26 of 33 children considered nontestable were assigned an MDI equivalent of <70 ($n = 23$) or $70+$ ($n = 3$). On the basis of the motor domain (scale 4) of the Vineland Adaptive Behavior Scales, 32 of 38 considered non-testable were assigned a PDI equivalent of <70 ($n = 27$) or $70+$ ($n = 5$).

Data Analysis

We evaluated the following 3 sets of hypotheses: (1) Congenital microcephaly predicts microcephaly at 2 years; (2) microcephaly at 2 years is associated with antecedent brain ultrasound lesions, including ventriculomegaly, and a hypoechoic lesion; and (3) microcephaly at 2 years is associated with neurodevelopmental dysfunctions at 24 months, even after considering antecedent head ultrasound evidence of white matter damage. We evaluated the last set of hypotheses by creating logistic regression models that include early information only (gestational age at birth, head circumference at birth, and ultrasound lesions) and then adding information that first became available later (head circumference at 24 months).

Results

The head circumferences at birth and at 24 months appear to be shifted modestly to the left of the normal distribution, with an overrepresentation of children whose head circumference is more than 2 SD below the expected mean, or Z-score < -2 (microcephaly). A total of 10% of infants in our sample had a birth head circumference Z-score < -2 , and 10% had a head circumference Z-score at 2 years that was < -2 . If the head circumference measure had a normal Gaussian distribution, 2.3% would have a Z-score < -2 .

Infants with congenital microcephaly were 3.5 times more likely to have microcephaly at 24 months post-term equivalent than infants who did not have microcephaly at birth (29% vs 8%) (Table I). Among the 78 children who had microcephaly at birth, a diminished birth weight Z-score was associated with an increased risk of a lower score on both the MDI and PDI portions of the BSID (data not shown). Children who had microcephaly at birth but not at 2 years did not have rates of dysfunction higher than those with normal head size at both birth and 24 months (Table II).

The risks of CP and an inability to walk even with assistance ($GMFCS \geq 2$) were substantially elevated in those with subnormal head size at 24 months, regardless of head circumference status at birth (data not shown). The head circumferences at 2 years of children with quadriparetic CP were appreciably smaller than those of children without CP (Figure, A and B; available at www.jpeds.com).

The risks of MDI < 70 or PDI < 70 were substantially elevated in those with subnormal head size at 24 months, regardless of head circumference status at birth (Table II) (Figure, C and D).

Because motor impairment might interfere with the M-CHAT screen, we restricted M-CHAT analyses to children who were able to walk independently ($GMFCS < 1$).¹¹ Those who screened

positive on the M-CHAT tended to have smaller head circumferences at birth and at 2 years than children who did not screen positive (Figure, E).

Overall, the risk of screening positive on the M-CHAT decreased with increasing head circumference at 24 months. Those with microcephaly at 24 months were nearly 3 times more likely to screen positive on the M-CHAT than infants who had macrocephaly (data not shown). By contrast, the risk of M-CHAT positivity did not vary appreciably with head circumference at birth (Table III; available at www.jpeds.com).

Because early ventriculomegaly can indicate the reversible effects of hemorrhage rather than the loss of white matter,²⁰ we conducted analyses that considered VM on the last ultrasound scan only, usually completed beyond 6 weeks after birth. Birth head circumference measures among infants with intraventricular hemorrhage, VM, and HL did not differ substantially from those who did not have any ultrasound abnormality (data not shown). By contrast, children who had late ventriculomegaly or hypoechoic lesions in cerebral white matter tended to have smaller head sizes at 24 months than children who had no ultrasound abnormality (Figure, F).

A head circumference Z-score < -2 supplemented ultrasound scan information that predicted CP risk and Bayley scale scores at 24 months (Table IV). This is evident among children who had either 1 or both of the sonographic indicators of white matter damage.

Compared with children who had neither sonographic evidence of cerebral white matter damage nor a head circumference Z-score < -2 , those with a single form of white matter damage and a smaller head circumference were at 10-fold the risk of CP, and a 2- to 3-fold elevated risk of a PDI < 70 or MDI < 70 . Children who had both white matter lesions (ie, ventriculomegaly and hypoechoic lesions) and a head circumference Z-score < -2 were at an 18-fold increased risk of CP and an almost 4-fold increased risk of an MDI or PDI below 70 compared with children whose head circumference was larger and who had no evidence of white matter damage.

We created multivariable models that included variables for ultrasound lesions and a head circumference Z-score < -2 at 24 months (Table V), as well as interaction terms. In each set of models, the ultrasound lesions (ie, ventriculomegaly or a hypoechoic lesion) provided significant information about each of the 3 dysfunctions evaluated. Adding a variable for head circumference Z-score < -2 at 2 years only minimally reduced the predictive information conveyed by the ultrasound lesions, while providing statistically significant additional information about the probability of each of the 3 outcomes. Adding an interaction term for the ultrasound lesions and the small head circumference altered the risk by only a small amount and inconsistently (data not shown).

Discussion

This large-scale, prospective study of ELGANs used algorithms to define CP diagnoses and considered brain ultrasound lesions in evaluating the risk of CP and cognitive impairment at 2 years associated with head circumference at birth and at 2 years. We report 3 novel findings. First, 71% of infants born with congenital microcephaly no longer were considered to have microcephaly at age 2 years. Second, congenital microcephaly is not a risk factor for CP or cognitive impairment unless the microcephaly persists. Finally, among children with microcephaly at 2 years, nearly a third have development of CP, and more than half have an MDI less than 70, rates that are approximately 3 times greater than among children who never had microcephaly.

Head circumference measures at birth and at 2 years in the ELGAN Study are modestly smaller than a reference sample, a finding also reported by others.²¹ Fewer than 3% of children with microcephaly born at term have a head circumference in the normal range at age 7 years (M. Klebanoff, National Collaborative Perinatal Project, Personal written communication, July 18, 2008). In contrast, we document that nearly three-fourths of ELGANs with congenital microcephaly in the ELGAN Study cohort had a normal head size at 2 years and neurodevelopmental outcomes that were not different from infants with normal head circumference at birth and at 2 years. Other studies that evaluated persistence of congenital microcephaly to later ages are birth weight based (less than 1500 g) and consequently have an overrepresentation of infants who were born small for gestational age.²²

Small head size at birth, in both term and preterm infants, reflects prenatal influences and is strongly associated with small for gestational age status.^{23,24} Normalization of head size in the preterm population may be ascribed to “catchup” head growth on a nutritional basis²⁴ or because of a resolution of an acute illness followed by a shift to an anabolic state.²⁵

Our finding that one third of children with microcephaly at age 2 have CP and more than half have an MDI less than 70 affirms the general observation of others that subnormal postnatal head growth is associated with lower MDI and IQ scores and poor school function, whether infants are born at term,²⁶ with very low birth weight,^{2,21,27} or now at extremely low gestational age.

Compared with children in the ELGAN Study who were not given a CP diagnosis, those given a diagnosis of CP were more than twice as likely to have a subnormal head size at 2 years, and those given a diagnosis of quadriparetic cerebral palsy were 5 times more likely to have a small head.¹² Because head circumference correlates with brain volume, children who have hemiparesis and especially quadriparetic can be assumed to have less brain tissue than the other children, including those with diparesis, who may have less severe brain tissue loss.²⁸

The high rate of microcephaly among extremely premature children who do not have CP suggests that brain tissue loss need not be expressed as a motor deficit at 2 years. We offer 2 explanations. First, whereas motor deficits likely involve pyramidal or extrapyramidal systems, brain lesions involving non-motor pathways manifest in other ways, such as with subnormal head size or cognitive deficits, both of which were overrepresented in children without CP in our cohort. Second, although motor impairment present earlier might become less apparent as a result of brain plasticity,²⁹ other manifestations of brain injury, including cognitive impairment, tend to persist.²⁹

Children with microcephaly were more than 2 times more likely to screen positive on the M-CHAT than children who did not have microcephaly and nearly 3 times more likely than children who had macrocephaly. Although 15% of children with idiopathic autism have macrocephaly by age 2 years, microcephaly, which also occurs in about 15% of children with autism spectrum disorder, appears to be especially common among the children who have a syndrome or a medical-genetic basis for their autism spectrum disorder.³⁰

Children who had late VM or HL lesions in cerebral white matter, presumably reflecting cerebral tissue loss, had smaller head sizes at 24 months than children who had no ultrasound abnormality, but the difference did not achieve statistical significance. This is similar to what has been seen in a low birth weight population.³¹ Two explanations may account for the lack of significance. First, given the relatively small numbers of children with these particular ultrasound lesions, the analyses likely were underpowered. Second, an appreciable amount of white matter damage is not identified by ultrasonography.^{32–34} White matter damage is seen only in about half of children who later have development of CP.²⁸

Although HUS evidence of white matter damage predicts CP,²⁸ and low MDI and PDI values,³⁵ information about a small head at 2 years appreciably supplemented this predictive/correlative capability. A likely explanation is that the most severe cerebral white matter damage tends to limit brain/head growth the most.

Among infants with congenital microcephaly, those who had a birth weight more than 2 SD below the mean had a lower MDI and PDI than their peers with microcephaly who had no evidence of fetal growth restriction, a finding reported by others.³⁶ This contrasts with the finding that children with symmetric growth restriction (ie, both head and body size are small) have better outcome than those who have asymmetric growth restriction (head size only is small).³⁷

Strengths of this study include the large sample of those at high risk for development of microcephaly, the high quality of ultrasound readings,¹⁶ standardized neurologic examination,^{12,14} including CD-ROM–based training about how to obtain optimal head circumference measures, an algorithm for diagnosing CP, and specific training for administering the Bayley Scales. In addition, defining the sample by gestational age rather than birth weight avoids overrepresentation of infants with fetal growth restriction.²²

The reported interobserver reliability of head circumference measures in neonates is 88% to 95%,^{38,39} and systematic bias is unlikely because those who measured the head at birth had no knowledge of later outcomes. On the other hand, accurate head circumference measures at birth may be distorted by scalp edema, head shape, and hair.⁴⁰ These distortions more likely would overestimate head size. In addition, we did not perform neuroimaging studies on these children at 2 years.

Additional limitations of this study are the lack of head circumference measures at discharge from the neonatal intensive care unit and absence of parental head size measures,⁴ but the prevalence of small head size in our cohort markedly exceeds any expected contribution to small head size by genetic predisposition.

In conclusion, we have found that ELGANs who have a small head at birth are not at increased risk of neurodevelopmental dysfunctions at 24 months post-term equivalent. In contrast, a small head at 2 years is associated with increased risks of neurodevelopmental dysfunctions and supplements prognostic information provided by cerebral white matter damage evident on neonatal HUS.

Glossary

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

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Head circumference at birth

A. Cerebral palsy

Quad: Quadriplegia, Di: Diparesis, Hemi: hemiparesis

Head circumference at 24 months

B. GMFCS

C. BSID PDI

D. BSID MDI **E. M-CHAT result among GMFCS < 1** **Head circumference at birth****F. Ultrasound finding** **Head circumference at 24 months** **Figure 1.**

Correlates of head circumference. These *box and whiskers* plots of head circumference at birth (on the left) and head circumference at 24 months post-term equivalent (on the right) identify the 25th percentile by the bottom of the box, the median by the *line* close to the middle of the box, and the 75th percentile by the top of the *box*. The dispersion of the head circumferences are indicated by the length of the vertical lines that emanate from the *box*, as well as by the *block dots*, which identify outliers. At 2 years, each type of CP is associated with microcephaly, although only association with quadriplegia reached nominal significance. Children who had microcephaly at age 2 years were also at increased risk of more severe motor impairment (higher GMFCS score) and low Bayley Scale scores.

Table 1
The percent of children classified by their head circumference Z-scores at birth and at 24-months corrected age

Head circumference Z-score at birth	Head circumference Z-score at 24 months				Row	
	< -2	$\geq -2, < -1$	$\geq 1, \leq 1$	$> 1, \leq 2$	> 2	N
< -2	29	31	37	3	0	78
$\geq -2, < -1$	15	25	49	9	2	224
$\geq 1, \leq 1$	8	15	61	12	5	516
$> 1, \leq 2$	4	14	49	29	5	108
> 2	0	13	50	16	22	32
Column N	101	175	522	118	42	958

These are row percents.

Table II

The percent of children classified by their head circumference at birth and 24 months who had each ultrasound finding and neurodevelopmental dysfunction listed

Microcephaly		Ultrasound		Neurodevelopmental dysfunctions				Row	
Birth	24 mo	HL	Late VM	CP	MDI < 70	PDI < 70	GMFCS 2+	N	
-	-	6	5	10	23	27	3	802	
+	-	2	8	2	22	27	0	55	
-	+	15	18	32	56	58	22	78	
+	+	4	9	26	70	83	22	23	
Column N		66	62	109	257	294	47	958	

Late VM, Ventriculomegaly on late (third) ultrasound scan.
These are row percents.

Table III

The risk of screening positive on the M-CHAT at 24 months corrected age among children classified by their head circumference Z scores at birth and at 24-months corrected age among those with GMFCS < 1

Head circumference Z-score at Birth	Head circumference Z-score at 24 months				
	≤ -2	> -2, ≤ -1	>1, <1	≥1, <2	≥2
≤ -2	31	8	16	0	—
≤ -1	18	29	18	16	0
>1, <1	15	17	17	10	13
≥1	50	25	16	20	0
≥2	—	0	24	0	0
Mean	22	20	17	13	8

These are cell-specific percents.

Table IV

The percent of children classified by their ultrasound finding and head circumference Z-score at 24 months who had each neurodevelopmental dysfunction

Ultrasound lesion		HC ₂₄ Z-score		Dysfunction at 24 months			Row
Late VM	HL	< -2		CP	MDI < 70	PDI < 70	N
-	-	-		5	21	24	739
-	-	+		18	55	55	78
-	+	-		26	33	46	39
-	+	+		67	50	83	6
+	-	-		34	38	44	32
+	-	+		78	67	89	9
+	+	-		86	57	79	14
+	+	+		86	100	100	7
Column N				108	249	287	924

Late VM, Ventriculomegaly on late (third) ultrasound scan; HC₂₄ Z-score, head circumference Z-score at 24 months.

These are row percents.

Table V

Risk ratios (and 95% confidence intervals) of CP, MDI < 70, and PDI < 70 in models that include a single ultrasound variable, that ultrasound variable and a variable for a small head at 24 months, or 2 ultrasound findings and microcephaly at 24 months

Model	Variables	Any CP	MDI < 70	PDI < 70
1	Late VM	15 (8.7, 27)	3.4 (2.0, 5.7)	4.5 (2.6, 7.8)
2	Late VM	14 (7.8, 25)	2.9 (1.7, 5.0)	4.1 (2.4, 7.0)
	HC ₂₄ Z-score < -1	3.3 (2.1, 5.2)	2.8 (2.0, 3.8)	2.0 (1.5, 2.7)
1	HL	13 (7.8, 23)	2.6 (1.6, 4.3)	4.1 (2.5, 7.0)
2	HL	12 (6.6, 20)	2.1 (1.3, 3.6)	3.6 (2.1, 6.2)
	HC ₂₄ Z-score < -1	3.1 (2.0, 4.8)	2.7 (2.0, 3.8)	1.9 (1.4, 2.6)
1	Late VM	11 (5.8, 20)	2.8 (1.6, 4.9)	3.5 (2.0, 6.1)
	HL	9.1 (5.0, 16)	2.0 (1.2, 3.4)	3.1 (1.8, 5.3)
2	Late VM	10 (5.3, 19)	2.6 (1.5, 4.5)	3.2 (1.8, 5.7)
	HL	8.0 (4.3, 15)	1.7 (0.96, 2.9)	2.8 (1.6, 4.8)
	HC ₂₄ Z-score < -1	3.0 (1.9, 4.7)	2.7 (2.0, 3.7)	1.9 (1.4, 2.6)

IVH, Intraventricular hemorrhage; *Late VM*, ventriculomegaly on late (third) ultrasound scan; *HC₂₄ Z-score*, head circumference Z-score at 24 months.

All models are adjusted for gestational age.