“Benign” Extra-axial Fluid in Survivors of Neonatal Intensive Care

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Objectives: To identify the prevalence of “benign” extra-axial fluid (BEAF), the risk factors associated with this condition, and the natural history in “graduates” of neonatal intensive care.

Design: Cross-sectional study.

Setting: Neonatal follow-up clinic at a tertiary care center.

Patients: Seventy-seven infants with a head circumference greater than the 95th percentile by growth percentiles from either the National Center for Health Statistics or the Infant Health and Development Program growth percentile graphs who attended the Neonatal Follow-up Program at The Children’s Hospital of Philadelphia between January 1, 1998, and December 31, 2001.

Main Outcome Measures: Bronchopulmonary dysplasia, extracorporeal membrane oxygenation; development at 18 to 24 months.

Results: There were 26 infants (34%) in the BEAF group, 43 (56%) in the control group without extra-axial fluid, and 8 (10%) in the hydrocephalus group. Compared with the control group, infants with BEAF were more likely to have bronchopulmonary dysplasia or to require use of extracorporeal membrane oxygenation in the immediate neonatal period (risk ratio, 6.1; 95% confidence interval, 1.5-29.8). Measurements of head circumference in the BEAF group showed rapid growth between 3 and 12 months, followed by growth greater than and parallel to the 95th percentile. Head circumference measurements in the control group showed continued growth along the 95th percentile for age. Infants with BEAF were more likely than controls to develop cerebral palsy (risk ratio, 9.9; 95% confidence interval, 1.3-77.9) and to have evidence of developmental delay at adjusted ages 12 and 18 to 24 months.

Conclusion: The presence of extra-axial fluid in macrocephalic survivors of neonatal intensive care is associated with an increased risk of developmental delay and cerebral palsy compared with control macrocephalic survivors.


RAPID HEAD GROWTH ACCOMPANIED by increased fluid in the subarachnoid space without evidence of ventricular enlargement or hydrocephalus characterizes “benign” extra-axial fluid (BEAF), also known as idiopathic external hydrocephalus. Since the advent of head computed tomography in the 1980s, more than 100 cases of BEAF have been reported in the literature. Prematurity and previous use of extracorporeal membrane oxygenation (ECMO) are 2 conditions that have been associated with BEAF. With improved survival rates in very low-birth-weight infants and term infants who require ECMO, the prevalence of BEAF, the risk factors associated with the development of this condition, and the natural history of neonates with BEAF have not been well described. This cross-sectional study of neonatal intensive care unit (NICU) survivors was designed to determine (1) the prevalence of BEAF in survivors with macrocephaly, (2) hospital risk factors associated with BEAF as the cause of macrocephaly, and (3) the natural history of survivors diagnosed as having BEAF compared with macrocephalic survivors without BEAF or hydrocephalus.

METHODS

STUDY POPULATION

Eligible infants were identified from neonates who visited the Neonatal Follow-up Program at The Children’s Hospital of Philadelphia between January 1, 1998, and December 31, 2001.
The Neonatal Follow-Up Program routinely saw all infants discharged from the NICU at The Children’s Hospital of Philadelphia who weighed 1500 g or less at birth or who weighed more than 1500 g and met one of the following criteria: perinatal depression, persistent pulmonary hypertension, grade 3 or higher intraventricular hemorrhage (IVH), cerebral infarction or periventricular leukomalacia, bronchopulmonary dysplasia (BPD), bacterial meningitis, small for gestational age, or need for ECMO. Perinatal depression was defined as a 5-minute Apgar score less than 3 and evidence of neurologic or multiple organ system involvement. This group of internal referrals made up approximately 50%, or 250, of the total number of infants followed. The remaining children were former premature or high-risk infants who were referred to the Neonatal Follow-Up Program by their primary pediatrician.

We identified all infants who visited the Neonatal Follow-Up Program whose head circumference was greater than the 95th percentile by standardized growth percentiles. Infants could be any age at the time of presentation. For infants whose birth weight was greater than 2500 g and whose gestational age was greater than 37 weeks, we used the growth percentiles developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion. For very low-birth-weight (<1500 g) and low-birth-weight (1501-2500 g) premature infants, we used growth percentiles developed by the Infant Health and Development Program. Classification of infants into the BEAF group, the control group without extra-axial fluid, or the hydrocephalus group was based on available radiologic data for all infants in the study. Approximately half of the infants underwent a head ultrasound, and the remainder underwent a computed tomographic or magnetic resonance imaging scan as their initial neurologic study. Further follow-up studies were performed as clinically indicated. Ventricular size was assessed using age-adjusted standard ratios for the diagnosis of hydrocephalus. Benign extra-axial fluid was diagnosed if there were large extra-axial spaces consistent with the subarachnoid space overlying the frontal lobes, which by observation looked larger than normal for an infant of that age. No evidence of tissue loss was seen in the brain either by reduction in cortex or white matter or by the presence of gliosis. Cerebrospinal fluid levels in the lateral, third, and fourth ventricles also needed to be normal. Before the statistical analysis, a masked independent radiologist (R.Z.) reviewed all of the neuroimages to confirm the diagnosis. No infant’s classification or diagnosis was changed as a result of the masked review.

DATA COLLECTION

After identification of eligible infants and approval from the institutional review board at The Children’s Hospital of Philadelphia, we retrospectively collected information about the hospital course from available office and hospital charts, including demographic information, need for ventilatory support or ECMO, and the presence of IVH, periventricular leukomalacia, seizures, meningitis, BPD, superior vena cava syndrome, or tracheostomy. Bronchopulmonary dysplasia was defined as an oxygen requirement at 28 days of age for term infants or at 36 weeks postconceptional age for preterm infants. Infants were then followed every 3 months during the first year of life and every 6 to 12 months during the next 2 years of life, after adjusting for gestational age at birth. Other visits were made when appropriate for the individual infants. Patients were “graduated” from the Neonatal Follow-Up Program after 12 months of age if either their medical and neuromotor problems had resolved or their problems had stabilized to such a degree that they could be cared for by their primary care practitioners, educators, and therapists in the community.

At each visit, weight, length, and head circumference were obtained. Standardized developmental testing using the Bayley Scales of Infant Development II was performed at 6, 12, and 18 to 24 months of age. If an infant had more than 1 developmental screening performed between ages 18 and 24 months, the latest visit was used in the analysis. We obtained standardized scores on the Mental Development Index and the Physical Development Index, with an average score of 100 and an SD of 13. Also, complete physical and neurologic examinations were performed at each visit. An infant was diagnosed as having cerebral palsy if he or she had tonal abnormalities that persisted to 12 to 18 months of age that affected the quality or acquisition of gross motor skills. Infants were followed until neurodevelopmental outcome was confirmed by clinical and developmental examinations. No infant who graduated from the Neonatal Follow-Up Program was subsequently diagnosed as having cerebral palsy.

STATISTICAL ANALYSIS

Mental Development Index and Physical Development Index scores were categorized as greater than or equal to 85 (normal), 70 to 84 (1 SD below the mean), and less than 70 (2 SD below the mean). For all categorical data, χ² or Fisher exact tests of equality, odds ratios, or risk ratios were calculated as appropriate. Continuous data were analyzed using an unpaired 2-tailed t test for independent samples. We used linear regression to predict the rate of weight, length, and head circumference growth for the BEAF and control groups after stratifying for the gestational age and sex of the infant. Because multiple measurements were taken from individual patients, we developed a random-effects time-dependent model, with adjusted age as the time variable and the patient as the random-effects variable. All statistical analyses were performed using a software program (STATA version 7.0; College Station, Tex).

RESULTS

Of 2031 children seen in 4 years, we identified 77 infants with head circumferences greater than the 95th percentile at a minimum of 1 visit to the Neonatal Follow-Up Program. The prevalence of macrocephaly in the patient population was 3.8%. Of the new patient referrals, 51% (1042) were from the NICU at The Children’s Hospital of Philadelphia. There were 26 infants (34%) in the BEAF group; 43 (56%), control group; and 8 (10%), hydrocephalus group. Because of the sparse number of infants with hydrocephalus in our cohort, these infants were excluded from further evaluation.

DEMOGRAPHICS AND HOSPITAL RISK FACTORS

There was a preponderance of male infants in the total group (42 [61%] of 69 infants), without a statistically significant difference in the percentage of male infants between the control and BEAF groups (Table 1). Neither mean gestational age nor mean birth weight was statistically significant between the 2 groups, although both groups had a bimodal distribution for these variables. Age at diagnosis was also similar in the groups. On examination of the hospital risk factors, more infants with BEAF had a diagnosis of BPD or required the use of ECMO. No other risk factors showed a statistically significant difference although more infants in the BEAF group were administered high-frequency ventilation and had a di-
BEAF Group
(n = 26)
Control Group
(n = 43)
Odds Ratio
(95% CI)

<table>
<thead>
<tr>
<th>Variable</th>
<th></th>
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<tbody>
<tr>
<td>BPD</td>
<td>10</td>
<td>4</td>
<td>6.1 (1.5-29.8)</td>
</tr>
<tr>
<td>ECMO</td>
<td>10</td>
<td>4</td>
<td>6.1 (1.5-29.8)</td>
</tr>
<tr>
<td>Male sex</td>
<td>14</td>
<td>38</td>
<td>1.6 (0.5-4.8)</td>
</tr>
<tr>
<td>HFOV during NICU stay</td>
<td>7</td>
<td>6</td>
<td>2.3 (0.6-9.4)</td>
</tr>
<tr>
<td>Any grade of IVH</td>
<td>11</td>
<td>12</td>
<td>1.9 (0.6-6.9)</td>
</tr>
<tr>
<td>Grade 3-4 IVH</td>
<td>1</td>
<td>1</td>
<td>1.7 (0-135)</td>
</tr>
<tr>
<td>PVL</td>
<td>3</td>
<td>4</td>
<td>1.3 (0.2-8.2)</td>
</tr>
<tr>
<td>Seizures</td>
<td>1</td>
<td>4</td>
<td>0.4 (0.01-4.3)</td>
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<tr>
<td>Gestational age, mean ± SD, wk</td>
<td>32.3 ± 5.1</td>
<td>32.7 ± 5.0</td>
<td>NA</td>
</tr>
<tr>
<td>Birth weight, mean ± SD, g</td>
<td>2053 ± 903</td>
<td>2273 ± 1294</td>
<td>NA</td>
</tr>
<tr>
<td>Age at diagnosis, mean ± SD, mo</td>
<td>6.5 ± 3.8</td>
<td>6.4 ± 5.1</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: BEAF, benign extra-axial fluid; BPD, bronchopulmonary dysplasia; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; HFOV, high-frequency oscillatory ventilation; IVH, intraventricular hemorrhage; NA, not applicable; NICU, neonatal intensive care unit; PVL, periventricular leukomalacia.

*Data are given as number of infants, except where indicated otherwise. All statistically significant comparisons are boldfaced.

NATURAL HISTORY

Weight, length, and head circumference were plotted on the appropriate growth curves for each infant. We then compared the measurements between the 2 groups. Weight and length for the BEAF and control groups were similar, but infants in the BEAF group had larger heads compared with the control group. As shown in the Figure, a rapid increase in the growth velocity of head circumference occurred between adjusted ages 3 and 12 months for infants with BEAF, rising to a point much greater than the 95th percentile. After this initial increase, the head circumferences for infants with BEAF paralleled the 95th percentile but remained significantly above it. Term macrocephalic infants with BEAF showed a more pronounced increase in head circumference during the first 12 months of life than preterm macrocephalic infants with BEAF. In contrast, the head circumferences of infants in the control group grew along the 95th percentile but barely rose above this level. There were no differences in the rate and degree of head circumference growth between male and female infants of similar gestational age and birth weight.

We constructed a linear regression model to further evaluate the rates of growth between the 2 groups after controlling for sex and gestational age. The model predicted macrocephalic infants with BEAF to have larger heads (average difference, 0.81 cm; 95% confidence interval [CI], 0.35-1.27 cm), lower weights (average difference, −0.67 g; 95% CI, −1.41 to 0.08 g), and shorter lengths (average difference, −1.12 cm; 95% CI, −2.89 to 0.65 cm) at any age.

Results of the 12-month and 18- to 24-month developmental follow-ups are given in Table 2. At the 12-month follow-up, statistically significantly more infants with BEAF had Mental Development Index scores less than 85, Mental Development Index scores less than 70, Physical Development Index scores less than 70, and hypotonia compared with the control cohort. Risk ratios for these variables ranged from 2.1 to 5.3. At the 18- to 24-month follow-up, more infants with BEAF had a Physical Development Index score less than 70 compared with the control cohort. The decreased number of infants seen at subsequent visits was the result of graduation of normally developed children from the program. Finally, a statistically significantly higher number of infants in the BEAF cohort were diagnosed as having cerebral palsy. All 6 of the infants with BEAF and cerebral palsy had a previous history of ECMO use; none of these infants had a neonatal history of IVH or periventricular leukomalacia.

SUBGROUP ANALYSIS

Because of the number of infants with BEAF and previous ECMO use who developed cerebral palsy, we evaluated the subgroup of infants who had macrocephaly and previous ECMO use. Fourteen infants with macrocephaly and neonatal use of ECMO were identified: 10 with BEAF and 4 controls. Four infants (29%) had a gestational age less than or equal to 37 weeks, and 3 of those infants had BEAF. No macrocephalic infant with a neonatal history of ECMO use had a diagnosis of hydrocephalus. One macrocephalic infant who received ECMO in the neonatal period had grade 1 IVH. Three infants who received ECMO had evidence of periventricular leukomalacia on neuroimaging during the neonatal period (2 in the BEAF cohort and 1 in the control cohort). Macrocephalic infants who required ECMO and developed BEAF had a lower birth weight (mean ± SD, 3191 ± 194 g vs 4040 ± 433 g) and received ECMO on more days (mean ± SD, 13.1 ± 4.8 days vs 6.8 ± 4.4 days) compared with macrocephalic infants who required ECMO and did not develop BEAF. Four of 10 infants with a discharge diagnosis of BPD received ECMO during their neonatal course.

COMMENT

This cross-sectional study identified 77 infants with head circumferences greater than the 95th percentile during a 3-year period. Benign extra-axial fluid was the cause of the macrocephaly in 26 (34%) of the NICU survivors seen in the follow-up program, and more infants with BEAF had a previous history of BPD or ECMO use in the immediate neonatal period. The extra-axial fluid collections seen in these infants was similar to the fluid collections previously termed “external hydrocephalus.” For the first 3 years of life, infants with BEAF had larger heads and similar weight and length compared with non-BEAF macrocephalic infants. The rate of increase was most rapid between 3 and 12 months of age after adjusting for gestational age, with the growth curves paralleling, but well above, the 95th percentile of the standardized growth percentiles after this time. Developmentally, infants with...
BEAF had a greater chance of gross motor delays and cerebral palsy by 12 to 18 months of life, especially if the infant required ECMO during the initial hospital course.

The association of ECMO and BPD with increased odds of BEAF in a population of macrocephalic NICU graduates is similar to that in other studies. Ment et al described 18 infants with evidence of BEAF, 6 of whom were preterm infants with a birth weight of 800 to 1230 g and a gestational age of 27 to 31 weeks. All 6 infants were referred for neurosurgical evaluation because their occipitofrontal measurements increased 3 growth percentiles. Unlike our population of patients, 4 of the 6 infants in the study by Ment et al experienced neonatal seizures. Extra-axial fluid collections have also been found in survivors of ECMO.

The natural history of BEAF in the macrocephalic NICU graduate differs from previously published studies concerning this condition in term neonates. The present study and other studies in term neonates show that the growth velocity of the head slows down and parallels the normal growth curve after the initial rapid increase. However, in our cohort of infants, BEAF was associated with a higher risk of developmental delay and cerebral palsy. These data were most striking in macrocephalic infants who received ECMO during their initial hospital course. In other studies, term infants who developed macrocephaly secondary to BEAF were not reported to have an increased risk of developmental delay or cerebral palsy. Our cohort of infants seems to be more similar to infants with extra-axial fluid collections resulting from bacterial meningitis, which may be associated with adverse neurologic outcomes. Our cohort, however, was drawn specifically from infants seen in a neonatal follow-up program at a tertiary care refer-

### Table 2. Results of Long-term Follow-up of BEAF and Control Infants

<table>
<thead>
<tr>
<th>Birth Weight</th>
<th>12-mo visit</th>
<th>18- to 24-mo visit</th>
<th>Cerebral palsy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BEAF Group</td>
<td>Control Group</td>
<td>Risk Ratio (95% CI)</td>
</tr>
<tr>
<td></td>
<td>MDI score &lt;85</td>
<td>12/20</td>
<td>5/22</td>
</tr>
<tr>
<td></td>
<td>MDI score &lt;70</td>
<td>4/20</td>
<td>0/22</td>
</tr>
<tr>
<td></td>
<td>PDI score &lt;85</td>
<td>14/18</td>
<td>10/21</td>
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<tr>
<td></td>
<td>PDI score &lt;70</td>
<td>9/18</td>
<td>2/21</td>
</tr>
<tr>
<td></td>
<td>Hypotonia</td>
<td>13/20</td>
<td>7/23</td>
</tr>
<tr>
<td></td>
<td>Abnormal DTR</td>
<td>6/20</td>
<td>3/23</td>
</tr>
<tr>
<td></td>
<td>18- to 24-mo visit</td>
<td>5/15</td>
<td>1/17</td>
</tr>
<tr>
<td></td>
<td>MDI score &lt;85</td>
<td>2/15</td>
<td>2/17</td>
</tr>
<tr>
<td></td>
<td>MDI score &lt;70</td>
<td>9/12</td>
<td>5/12</td>
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<tr>
<td></td>
<td>PDI score &lt;85</td>
<td>7/12</td>
<td>2/12</td>
</tr>
<tr>
<td></td>
<td>PDI score &lt;70</td>
<td>8/26</td>
<td>1/43</td>
</tr>
</tbody>
</table>

Abbreviations: BEAF, benign extra-axial fluid; CI, confidence interval; DTR, deep tendon reflexes; MDI, Mental Development Index; NA, not applicable; PDI, Physical Development Index.

*Data are given as number of patients with variable/total number of patients followed up. All statistically significant associations are boldfaced.

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Benign extra-axial fluid has been associated with macrocephaly in NICU graduates. Although term macrocephalic infants without other risk factors have not been reported to have an increased risk of developmental delay, this condition has not been studied in a high-risk population.

Macrocephalic infants with BEAF were more likely to have BPD or to have previously used ECMO. These infants were also more likely to develop developmental delay at ages 12 and 18 to 24 months. Macrocephaly due to BEAF in NICU graduates should lead to a developmental assessment and the provision of appropriate early intervention services to these infants.

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REFERENCES