Early Human Development 91 (2015) 187–193

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Patient characteristics are important determinants of neurodevelopmental outcome during infancy in giant omphalocele

Enrico Danzer [a,b,*], Marsha Gerdes [a,b], Jo Ann D'Agostino [a,b], Judy Bernbaum [a,b], Casey Hoffman [a,b], Natalie E. Rintoul [a,b], Lisa M. Herkert [a,b], Alan W. Flake [a,b], N. Scott Adzick [a,b], Holly L. Hedrick [a,b]

[a] The Center for Fetal Diagnosis and Treatment, The Children's Hospital of Philadelphia, Philadelphia, PA, USA
[b] The Perelman School of Medicine, The University of Pennsylvania, USA

ARTICLE INFO

Article history:
Received 23 September 2014
Received in revised form 26 December 2014
Accepted 28 December 2014

Keywords:
Giant omphalocele
Neurodevelopmental outcome
Bayley Scales of Infant Development
Autism
Pulmonary hypoplasia

ABSTRACT

Objective: To examine patient-specific factors as potential predictors of neurodevelopmental (ND) outcome in children with giant omphalocele (GO).
Materials: Between 06/2005 and 07/2012, 31 consecutive GO survivors underwent ND assessment using the BSID-III at a median of 24 months (range 6–35). ND delay was defined by a score of ≤84 in any composite score. Severe impairments were defined as a score of ≤69 in at least one domain. Correlations between ND outcome and patient-specific factors were analyzed by one-way ANOVA, chi-square, or logistic regression as appropriate.
Results: The mean cognitive score (86.8 ± 16.8) was in the low average range. Mean language (83.2 ± 21.1) and motor (81.5 ± 16.2) scores were below average. Forty-six-percent scored within the average range for all scales. Mild deficits were found in 19%, and 35% had severe delays in at least one domain. Hypotonicity was present in 55%. Autism was suspected/confirmed in 13%. Predictors of lower ND scores were prolonged ventilator support ($P < 0.01$), high-frequency oscillatory ventilation ($P < 0.01$), tracheostomy placement ($P < 0.001$), O_2 supplementation at day of life 30 ($P < 0.02$), pulmonary hypertension ($P < 0.02$), delayed enteral feeding ($P = 0.01$), need for feeding tube ($P < 0.001$), GERD ($P = 0.05$), abnormal BAER hearing screen ($P < 0.006$), prolonged hospitalization ($P = 0.01$), and failure to thrive ($P = 0.001$). Autism was associated with delays in cognitive and language outcomes ($P < 0.03$). Delayed staged closure ($P = 0.007$), older age at final repair ($P = 0.03$), and hypotonicity ($P = 0.02$) were associated with motor dysfunction.
Conclusions: Neurological impairments were present in more than half of GO survivors. Disease severity was associated with ND dysfunction. Autism and hypotonicity were often co-morbidities with ND delays and poor motor function.

1. Introduction

Omphalocele refers to an anatomical anomaly of the abdominal wall in which there is herniation of abdominal contents into a membrane-covered sac. It is generally classified into small, giant, and ruptured, depending on the size of the abdominal defect and/or its content. Giant omphalocele (GO) is defined as a defect that contains the majority of the liver (>75%), resulting in a significant loss of abdominal domain and an underdeveloped peritoneal cavity [1–3].

Postnatal survival of GO at tertiary centers has improved dramatically with reported rates of 70% to 90% [2–4]. With improved survival there has been an increasing focus on associated short- and long-term morbidity [1,4]. This has led to the troubling recognition that neurodevelopmental dysfunction is one of the most common, and potentially most disabling, complication for children with GO [2,5,6]. We previously showed that more than 50% of GO survivors are identified with various degrees of cognitive disabilities, language, and motor problems during infancy [2]. These early neurodevelopmental problems may ultimately affect academic achievements, may significantly decrease quality of life for children with GO and their families, and may result in significant costs to society.

The etiology of adverse neurodevelopmental outcome in GO is likely multifactorial with the precise role of specific medical, surgical, and socio-demographic factors not fully delineated. Evaluation of predictors of outcome is critical so that support resources can be targeted to those at highest risk of neurodevelopmental disability. An improved understanding of the pathophysiological pathways and the neurodevelopmental consequences will allow earlier interventions which in turn may help treat neurological morbidities before additional disabilities evolve, may reduce the incidence of adverse outcomes, and may improve long-term academic achievements. Given the small

* Corresponding author at: The Center for Fetal Diagnosis and Treatment, The Children's Hospital of Philadelphia, 5th Floor Wood Center, 3615 Civic Center Blvd, Philadelphia, PA 19104-4318, USA. Tel.: +1 215 590 2733; fax: +1 215 590 2447.
E-mail address: danzere@email.chop.edu (E. Danzer).

http://dx.doi.org/10.1016/j.earlhumdev.2014.12.009
0378-3782/

sample size of the currently available outcome studies and therefore the inability to perform meaningful statistical analysis, one of the major challenges for perinatologists, neonatologists, and pediatric surgeons involved in the care and treatment of GO patients is to prognosticate neurodevelopmental outcome to provide appropriate counseling for affected families and planning for the care of these children throughout childhood.

The ability to identify neonates at increased risk for adverse neurodevelopmental outcome would be useful as the numbers of surviving GO infants continue to increase. By using review of prospectively acquired data, the current study was undertaken to report the early ND outcome of a relatively large cohort of GO patients and to identify patient-specific factors and management variables as predictors of adverse ND outcome in GO.

2. Material and methods

2.1. Ethics statement

The Institutional Review Board, Committee for Protection of Human Subjects of The Children's Hospital of Philadelphia approved this study and all parents or legal guardians gave written informed consent for their children (IRB 2004-5-3779).

2.2. Patient population

This was a review of prospectively collected data on neurodevelopmental and neurofunctional outcomes in GO survivors enrolled in our follow-up program between June 2005 and July 2012. All GO survivors born during the study period were eligible. GO was defined as a large abdominal evisceration with a covering membrane containing the majority (>75%) of the liver. This definition was established by consensus of our pediatric surgeons, as definitions dependent on measurement of the defect were not considered useful, since a large amount of abdominal viscera and liver may be eviscerated even through a narrow defect in the abdominal wall [1–3]. Among this cohort, subjects who were at least 6 months of age and underwent neurodevelopmental assessment were identified; this group forms the study population for the current report. The study group included premature infants, low birth weight as well as full term, normal weight GO survivors with or without additional minor (e.g. inguinal hernia, undescended testes, 2-vessel cord, IUGR) or major (e.g. congenital diaphragmatic hernia, congenital cardiac defects) congenital malformations.

2.3. Perinatal and postnatal management

Our standardized protocol for the perinatal and postnatal management of patients with prenatally diagnosed GO has been described elsewhere [1–3]. Briefly, the initial evaluation included detailed fetal ultrasonography and ultrafast MR imaging. Assessment included confirmation of the diagnosis and assessment for other anomalies. Fetal echocardiography and Doppler flow measurements were performed to assess cardiac anatomy and function. After evaluation, all patients underwent nondirective counseling for pregnancy management options. The options included (1) termination of pregnancy if the gestational age was less than 24 weeks and (2) standard postnatal care with prenatal ultrasound surveillance and cesarean delivery.

In GO newborns, the postnatal ventilator management in the neonatal intensive care unit has been described elsewhere [7–9]. The mode of ventilation is aimed at administering only enough pressure to maintain preductal oxygen saturations greater than 85% or postductal PaO_2 greater than 30 mm Hg. High frequency ventilation is reserved for neonates that continue to have hypercapnia refractory to conventional ventilation. Lung preservation ventilation strategies, nitric oxide, and sildenafil are used to treat pulmonary hypertension. Echocardiography is performed early to establish the presence and severity of pulmonary hypertension. The operating surgeon determines the type of repair (e.g. staged reduction and closure, or "paint and wait") based upon co-morbidities and whether the newborn is stable enough for surgical intervention [2,3].

2.4. Data collection

Perinatal, perioperative and postnatal factors that might affect neurodevelopmental outcome such as gestational age at delivery, birth weight, APGAR scores, ventilator management, type of surgical closure, age at first and last closure procedure, number of surgical reductions, duration of total parenteral and nasogastric feeding, time to first oral feeding, O_2 requirement at day of life 30, length of stay, and major complications during initial admission, length of stay, and other clinical parameters were obtained from maternal prenatal charts and neonatal hospital records.

2.5. Follow-up and neurodevelopmental assessment

Growth parameters including weight, length, and head circumference were measured and compared to standard reference curves. Corrected age was used to plot measurements for preterm infants. The child's race and ethnicity were assessed by parental report.

Developmental assessment of study participants during infancy was performed using the Bayley Scales of Infant Development, 3rd Edition (BSID-III). The third edition of the BSID was published in 2006 and has been validated in at-risk populations between ages 1 and 42 months [10]. BSID-III provides composite scores for cognitive, language, and motor outcomes. The normalized population mean and SD of each composite score is 100 ± 15. The cognitive scale contains items that assess memory, problem solving, and counting skills. The language scale evaluates both receptive and expressive language; evaluating the child's understanding and use of words and gestures. The motor scale assesses fine (e.g. dexterity) and gross (e.g. walking) motor skills. Overall scores were grouped as average, borderline, and delayed based on SD intervals (85–115, 70–84, and $\leq$69, respectively). If a child was judged to be too developmentally impaired to complete the tasks, a score was imputed by assigning him or her the lowest possible score for the specific test. The neuromuscular examination (active tone, passive tone, reflexes, gross motor abilities, and fine motor abilities) was classified as normal if no abnormalities affecting motor skills were noted, suspect if a moderate degree of abnormality was noted, and abnormal if functionally significant abnormalities of tone, reflexes, or motor skills were present.

Autism diagnosis was made based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV [11]) guidelines by clinical evaluations by either psychiatrist, developmental pediatrician or psychologist who used the Autism Diagnostic Observation Schedule (ADOS) or Autism Diagnostic Interview (ADI).

2.6. Definition of neurodevelopmental delay

In order to capture the majority of GO survivors who would be expected to experience at least some degree of impairments, neurodevelopmental delay was defined by a score of $\leq$85 in any of the evaluated composite scores. Further severe impairments were defined as a score of $\leq$69 in at least one domain tested.

2.7. Statistical analysis

The differences between groups were determined using a chi-square test, Student's t test, Wilcoxon rank-sum, one-way ANOVA, or Kruskal–Wallis non-parametric one way ANOVA, depending on the outcome variable and number of groups. Prediction of outcome variables used