Journal of Pediatric Surgery 52 (2017) 437–443

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

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

Neurodevelopmental outcomes at 5 years of age in congenital diaphragmatic hernia

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ARTICLE INFO

Article history:
Received 29 December 2015
Received in revised form 4 August 2016
Accepted 22 August 2016

Key words:
Congenital diaphragmatic hernia
Neurodevelopmental outcome
Behavioral problems
Autism
Pulmonary hypoplasia
Pulmonary hypertension
Socioeconomic status

ABSTRACT

Objective: To evaluate neurodevelopmental sequelae in congenital diaphragmatic hernia (CDH) children at 5 years of age.

Materials and methods: The study cohort of 35 CDH patients was enrolled in our follow-up program between 06/2004 and 09/2014. The neurodevelopmental outcomes assessed at a median of 5 years (range, 4–6) included cognition (Wechsler Preschool and Primary Scale of Intelligence [WPPSI], n = 35), Visual-Motor-Integration (n = 35), academic achievement (Woodcock-Johnson Tests of Achievement, n = 25), and behavior problems (Child Behavior Check List [CBCL], n = 26). Scores were grouped as average, borderline, or extremely low by SD intervals.

Results: Although mean Full (93.9 ± 19.4), Verbal (93.4 ± 18.4), and Performance (95.2 ± 20.9) IQ were within the expected range, significantly more CDH children had borderline (17%) and extremely low (17%) scores in at least one domain compared to normative cohorts ($P < 0.02$). The Visual-Motor-Integration score was below population average ($P < 0.001$). Academic achievement scores were similar to expected means for those children who were able to complete testing. CBCL scores for the emotionally reactive (23%) and pervasive developmental problems scales (27%) were more likely to be abnormal compared to normal population scores ($P = 0.02$ and $P = 0.0003$, respectively). Autism was diagnosed in 11%, which is significantly higher than the general population ($P < 0.01$). Univariate analysis suggests that prolonged NICU stay, prolonged intubation, tracheostomy placement, pulmonary hypertension, autism, hearing impairment, and developmental delays identified during infancy are associated with worse cognitive outcomes ($P < 0.05$).

Conclusion: The majority of CDH children have neurodevelopmental outcomes within the average range at 5 years of age. However, rates of borderline and extremely low IQ scores are significantly higher than in the general population. CDH survivors are also at increased risk for developing symptoms of emotionally reactive and pervasive developmental problems. Risk of autism is significantly elevated. Disease severity and early neurological dysfunction appear to be predictive of longer-term impairments.

Survival rates for neonates born with congenital diaphragmatic hernia (CDH) have improved significantly over the past 2 decades [1]. Innovation in surgical techniques and perioperative care are important contributors. With improved survival, however, it has been increasingly recognized that neurocognitive disabilities and impaired functional outcomes are common in these patients. Indeed neurodevelopmental dysfunction has become the most common and potentially the most disabling outcome of CDH and its treatment during infancy [2–8]. Most CDH survivors have multi-organ involvement and may require prolonged recovery periods. As a result neurofunctional outcome may be delayed early in life [9]. On the other hand, the predictive value of neurodevelopmental testing during infancy is limited as the extent of impairment is often not fully recognized until later in childhood when complex cognitive and academic skills are required.

Only a few studies have focused on the developmental outcomes in CDH during preschool and/or early school age [10–13]. An improved understanding of which CDH patients are at risk of longer-term neurodevelopmental disabilities is critical for counseling and for the provision of early intervention for affected individuals [5].

The current study was undertaken to: (1) assess neurodevelopmental performance at kindergarten age in multiple domains compared to normative data and (2) evaluate potential risk factors of

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http://dx.doi.org/10.1016/j.jpedsurg.2016.08.008
0022-3468/

adverse cognitive and behavioral outcomes in a contemporary CDH population.

1. Material and methods

1. Ethical 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. Patient population

We retrospectively evaluated prospectively collected data on developmental outcomes in CDH survivors enrolled in our multidisciplinary follow-up program, the Pulmonary Hypoplasia Program, between June 2004 and September 2014. All CDH survivors born during the study period who enrolled in the follow-up program were eligible. Among this cohort, subjects who underwent neurodevelopmental evaluations between the fourth and sixth birthday were identified and form the study population.

3. Perinatal management

As previously described, CDH patients are treated according to a specific perinatal and postnatal management protocol [1,3–5,14]. Briefly, all CDH patients referred to The Center for Fetal Diagnosis and Treatment at The Children's Hospital of Philadelphia undergo a comprehensive prenatal imaging evaluation (ultrasonography, echocardiography, MR imaging). After evaluation, all patients undergo nondirective counseling for pregnancy management options. The postnatal ventilatory management in the neonatal intensive care unit utilizes a lung-preservation strategy similar to that of infants with other causes of pulmonary hypoplasia (e.g. giant omphalocele, fetal lung lesions) [1,14–16]. High frequency ventilation is generally reserved for neonates that continue to have hypercapnia refractory to conventional ventilation. Indication for initiation of extracorporeal membrane oxygenation (ECMO) therapy includes failure of medical management to avoid ventilator-related lung injury or persistent hypotension/acidosis. The operating surgeon determines the timing of repair based upon co-morbidities and clinical stability as well as the need for patch repair based upon the size of the diaphragmatic defect. Perinatal, perioperative, and postnatal factors that might independently affect neurodevelopmental and neurobehavioral outcome were obtained from maternal prenatal and neonatal hospital records.

4. Socioeconomic status

Socioeconomic data, such as marital status, level of parental education, employment status, and overall annual household income were collected by interview with a parent or guardian at the time of enrollment.

5. Neurodevelopmental testing

To provide a broad assessment of neurodevelopmental status, multiple domains were tested including cognition, visual motor skills, early academic achievement, and a wide range of behavior problems [3,10,17].

Cognitive outcomes were assessed using the Wechsler Preschool and Primary Scale of Intelligence, Third Edition and Fourth Edition (WPPSI-III, WPPSI-IV), and information was utilized from three composite scores: Verbal intelligence quotient (Verbal-IQ) estimates verbal reasoning and comprehension and attention to verbal stimuli [18]. Performance intelligence quotient IQ (Performance IQ, Visual–Spatial Reasoning in the WPPSI-IV) estimates nonverbal reasoning, including spatial processing and perceptual organization. Full Scale IQ (Full-IQ) is a summary score reflecting multiple aspects of cognitive processing. Each of the composite scores has an expected mean of 100 and a standard deviation (SD) of 15. Scores were grouped as average, borderline, and delayed based on SD intervals (85–115, 70–84 [1 SD below mean], ≤69 [2 SD below mean], respectively).

Visual-motor integration was assessed with the Developmental Test of Visual Motor Integration (VMI), a copying task that assesses the child's fine-motor and visual-motor coordination skills [19]. The average VMI score is 100 ± 15, with higher scores indicating better performance.

Academic achievement (school readiness for reading and math) was tested using the reading and math clusters of the Woodcock-Johnson Psychoeducational Battery-Revised (WJPBR) and the Woodcock Johnson Tests of Achievement Fourth Edition, a standardized achievement test for children from 2 years to adulthood [20]. The academic achievements are scaled with a mean of 100 ± 15.

Behavioral difficulties were assessed using the Child Behavior Checklist (CBCL) for ages 1.5 to 5 years, which is a questionnaire used to obtain parental reports of behavior problems demonstrated in the home within the previous 6 months across internalizing and externalizing domains. Ratings are compiled into seven subscales including: Emotionally Reactive, Anxious/Depressed, Somatic Complaints, Withdrawn, Sleep Problems, Attention Problems, and Aggressive Problems. In addition, five DSM-IV subscales are computed, which are not diagnostic, but indicate that some symptoms of the disorders may be present. These include: Affective Problems, Anxiety Problems, Pervasive Developmental Problems, Attention Deficits/Hyperactivity Problems, and Oppositional Defiant Problems [21].

The Pervasive Developmental Problem scale assesses the prevalence of symptoms in the area of reciprocal social interactions and restricted behaviors (e.g. repetitive behavior or disturbed by change). This scale was developed to incorporate some of the behavioral symptoms that the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, lists as criteria for the diagnosis of an autism spectrum disorder (autism, Asperger syndrome, or pervasive developmental disorder not otherwise specified) [22]. High scores on the Pervasive Developmental Problem Scale do not confirm the diagnosis of an autism spectrum disorder but suggest that further evaluation is warranted.

If a child was judged to be too developmentally impaired to complete the tasks, he/she was assigned the lowest possible score for the specific test; if a child was unable to complete the task for other reasons (e.g. unwillingness of the child and/or parents to participate, child older than 5 years of age for CBCL testing); the child was excluded from the analysis for that domain.

6. Definition of neurodevelopmental delay

As previously reported [10,23], in order to capture the majority of CDH survivors who would be expected to experience at least some degree of impairment, neurodevelopmental delay was defined by a score of ≤85 in any of the evaluated composite scores. Severe impairment was defined as a score of ≤69 in at least one domain tested.

7. Statistical analysis

Continuous data are presented as means ± SD (median, range). Categorical data are presented as proportions. The differences between developmental outcomes were determined using Student's t, one-way ANOVA, chi-square, or linear regression, depending on the type of outcome variable. Prediction of outcome variables used logistic regression, or ordinal logistic regression, depending on the type of outcome variable. One-sample t-test was used to compare the mean outcome scores to the population mean. *P* values less than .05 were considered statistically significant and were not corrected for multiple tests. All analyses were conducted in STATA version 12.0 (College Station, TX, USA).