Journal of Pediatric Surgery 51 (2016) 1627–1634

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

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

Neurocognitive outcomes in congenital diaphragmatic hernia survivors: a cross-sectional prospective study☆,☆☆,★

Katarina Bojanić [a,1], Marina Grubić [b], Ana Bogdanić [b], Jurica Vuković [b], Toby N. Weingarten [c], Andrea R. Huebner [d], Juraj Sprung [c,*], Darrell R. Schroeder [e], Ruža Grizelj [b,1,2]

[a] Division of Neonatology, Department of Obstetrics and Gynecology, University Hospital Merkur, Zagreb, Croatia
[b] Department of Pediatrics, University of Zagreb, School of Medicine, University Hospital Centre Zagreb, Croatia
[c] Mayo Clinic, Rochester, MN, USA
[d] Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN, USA
[e] Department of Health Sciences Research, Division of Biostatistics, Mayo Clinic, Rochester, MN, USA

ARTICLE INFO

Article history:
Received 1 February 2016
Received in revised form 17 May 2016
Accepted 20 May 2016

Key words:
Congenital diaphragmatic hernia
Cross-sectional study
Early learning composite score, ELC
Full scale IQ, FSIQ
Mullen Scales of Early Learning, MSEL
Wechsler Intelligence Scale–Fourth Edition, WISC-IV

ABSTRACT

Background/purpose: Congenital diaphragmatic hernia (CDH) survivors may have persistent neurocognitive delays. We assessed neurodevelopmental outcomes in CDH survivors from infancy to late teenage years.
Methods: A cross-sectional study was conducted on 37 CDH survivors to examine neurocognitive functioning. Overall cognitive score was tested with the early learning composite (ELC) of Mullen Scales of Early Learning ($n = 19$), and Full Scale IQ (FSIQ) of Wechsler Intelligence Scale for Children–Fourth Edition ($n = 18$).
Results: ELC was 85.7 ± 16.4, lower than the expected norm of 100, $P = 0.004$, and 6 survivors had moderate, and 3 severe delay, which is not greater than expected in the general population ($P = 0.148$). FSIQ was 99.6 ± 19.1, consistent with the expected norm of 100, $P = 0.922$, and 3 survivors had moderate and 2 severe delay, which is greater than expected ($P = 0.048$). Although ELC was lower than FSIQ ($P = 0.024$), within each testing group overall cognitive ability was not associated with participant age (ELC, $P = 0.732$; FSIQ, $P = 0.909$). Longer hospital stay was the only factor found to be consistently associated with a worse cognitive score across all participants in our cohort.
Conclusions: A high percentage of survivors with CDH have moderate to severe cognitive impairment suggesting that these subjects warrant early testing with implementation of therapeutic and educational interventions.
Published by Elsevier Inc.

Neurodevelopmental impairment represents a significant residual morbidity in congenital diaphragmatic hernia (CDH) survivors [1–4]. Poor neurodevelopmental outcomes very likely have a multifactorial etiology, some related to acuity of CDH presentation [4–9], and others to CDH associated structural brain lesions [10]. By age 3, 88% of CDH survivors evaluated with magnetic resonance imaging (MRI) had some type of abnormal intracranial findings [10,11]. In addition, it has been shown that the MRI-assessed cerebral maturation is slower in CDH infants compared to healthy age-matched infants [12]. Whether these findings have direct link to neurodevelopmental outcomes of CDH survivors is not known.

Several investigators have examined neurodevelopment in CDH survivors [1–4,6,7,12–14], most during the first several years of life, but rarely in late adolescence [3]. It has been shown that CDH survivors remain at risk for neurocognitive delay at school age, and certain postnatal factors, mostly related to the severity of CDH (e.g., need for extracorporeal membrane oxygenation [ECMO]) predict later cognitive difficulties [1,5]. The primary objective of our cross-sectional study was to describe neurocognitive outcomes in CDH survivors ranging in age from infancy to 16 years. The secondary objective was to explore the potential association of birth and CDH characteristics with neurocognitive outcomes.

1. Material and methods

1.1. Ethics statement

This study was approved by the Institutional Ethics Committee of the University Hospital Centre (UHC) Zagreb, Croatia and written informed consent was obtained from all patients and their parents prior to participation.

Abbreviations: CDH, congenital diaphragmatic hernia; ECMO, extracorporeal membrane oxygenation; EL, Expressive Language scale; ELC, early learning composite score; FM, fine motor scale; FSIQ, full-scale IQ; GM, gross motor scale; IQ, intelligence quotient; MRI, magnetic resonance imaging; MSEL, Mullen Scales of Early Learning; OCS, overall cognitive score (includes ELC and FSIQ); PRI, Perceptual Reasoning Index; PSI, Processing Speed Index; RL, receptive language scale; VCI, Verbal Comprehension Index; VR, visual reception scale; WMI, Working Memory Index; WISC-IV, Wechsler Intelligence Scale for Children–Fourth Edition.

☆ Conflicts of interest: none.
☆☆ Sources and support for the work: This project was supported by internal funding from the Department of Anesthesiology, Mayo Clinic Rochester, Minnesota.
★ Cooperative study: The testing was entirely done at University Hospital Centre (UHC), Zagreb, Croatia, analysis of data and writing the manuscript were done both at UHC and Mayo Clinic, Rochester, Minnesota.

* Corresponding author at: Department of Anesthesiology, Mayo Clinic, 200 First St SW, Rochester, MN, USA 55905. Tel.: +1 507 255 3298; fax: +1 507 255 6463.
E-mail address: sprung.juraj@mayo.edu (J. Sprung).
[1] Equal contributors.
[2] Senior author.

http://dx.doi.org/10.1016/j.jpedsurg.2016.05.011
0022-3468/Published by Elsevier Inc.

1.2. Patient population

The study was conducted at Croatia's largest referral center for neonates with CDH. All subjects in this study were outborns since UHC Zagreb does not have a maternity ward. All infants born with CDH who were treated between January 1990 and February 2015, and were less than 17 years old as of May 1, 2015, were considered eligible to participate in this study. ECMO was unavailable in Croatia during the study timeframe; therefore none of survivors received ECMO treatment.

1.3. Data collection

Demographic, neonatal, and postnatal characteristics were extracted from the medical records. The variables considered were: prenatal CDH diagnosis, sex, weight (birth weight and weight at 1 year), head circumference (at birth and at 1 year), gestational age, admission capillary blood carbon dioxide tension ($PcCO_2$), associated congenital anomalies, surgery timing, duration of mechanical ventilation, length of hospitalization, and bronchopulmonary dysplasia [15]. We collected information regarding *early presentation* (respiratory distress evident immediately after delivery) and *late presentation of CDH* (respiratory distress delayed >6 hours after delivery) as well as whether the liver was herniated into the chest (liver-up). Probability of survival (POS) was assessed from an equation proposed by the Congenital Diaphragmatic Hernia Study Group [16], to categorize neonates into 3 POS score groups based on birth weight and 5-minute Apgar score: low (0–33%), moderate (34–66%), and high (67–100%) predicted survival groups. Patients were also categorized as having "low", "intermediate" or "high" risk of death based on birth weight, Apgar score, presence of severe pulmonary hypertension, cardiac and chromosomal anomalies according to the Brindle risk score [17].

Growth measurements included weight and head circumference at birth and at age 1 using the 2006 WHO Growth Standard charts to report growth metric percentiles and *Z*-scores on children from 0 to 24 months of age [18]. Head occipito-frontal circumference was measured during the initial hospitalization and at age 1 measuring the widest horizontal circumference of the head. For premature neonates we used 2013 Fenton growth charts until 50 weeks postmenstrual age and afterwards corrected age was used to plot measurements on WHO growth charts [19]. We analyzed the difference in head circumference *Z*-scores from birth to 1 year of age, and difference in weight *Z*-scores from birth to 1 year of age and compared these measurements to neurodevelopmental outcomes.

Experienced neonatologists reviewed serial postnatal head ultrasound scans performed during the initial hospitalization and Papile [20] classification was used to grade the severity of intraventricular hemorrhage (IVH). Head ultrasound findings were classified as *normal*—normal intra- or periventricular echodensity or echolucency and a normal size of the ventricular system or minor abnormalities (e.g. plexus cysts, subependymal pseudocysts); *mildly abnormal*—presence of a IVH grade I or II; *moderately abnormal*—IVH grade III; and *severely abnormal*—IVH grade IV, cystic periventricular leukomalacia, enlargement of extracerebral cerebrospinal fluid space, ex-vacuo ventriculomegaly.

1.4. Neurodevelopmental assessment

All children were tested by two licensed board certified child psychologists. If born preterm (<37 weeks' gestation) and the assessment was completed prior to the second birthday the scores were calculated based on the adjusted age. Neurodevelopment was assessed with the Mullen Scales of Early Learning (MSEL) for children younger than 68 months, and the Wechsler Intelligence Scale for Children–Fourth Edition (WISC-IV) for participants 6 to 16 years and 11 months.

1.4.1. The Mullen Scales of Early Learning

The MSEL is a comprehensive measure of cognitive and motor functioning and uses standardized cognitive assessment that consists of 5 individual scales: 4 cognitive scales (visual reception [VR], fine motor [FM], receptive language [RL], and expressive language [EL] scale), and 1 gross motor (GM) scale administered to children from birth to 33 months. Each of the scaled scores has a mean of 50 and an SD of 10 and scores may range between 20 and 80 (average: mean ± 1 SD = 40–60; below average [moderately impaired]: >1 SD–2 SD below the average = 30–39; significantly below average [severely impaired]: >2 SD below average <30). The 4 cognitive scales can be combined to produce an overall score, i.e., *early learning composite score (ELC)* that represents general intelligence. ELC has a mean of 100 and an SD of 15, and scores between 70 and 84 are considered moderately delayed, while scores <70 are considered severely delayed.

1.4.2. Wechsler Intelligence Scale for Children–Fourth Edition

WISC-IV provides a *Full-Scale IQ (FSIQ)* to represent a child's overall cognitive ability [21]. In addition, 4 composite scores are derived to represent functioning in more discrete cognitive domains: the Verbal Comprehension Index-VCI, the Perceptual Reasoning Index-PRI, the Working Memory Index-WMI and the Processing Speed Index-PSI. FSIQ and each of the composite scores have a mean of 100 and an SD of 15 with a score between 70 and 84 denoting moderate delay, and <70 severe delay.

1.5. Statistical analyses

Perinatal characteristics of CDH survivors who did and did not participate in this study are summarized using mean ± SD or median [25th, 75th percentile] for continuous variables, and frequency percentages for categorical variables. Groups were compared using the two-sample t-test, or Wilcoxon rank sum test, for continuous variables and the chi square test, or Fisher's exact test, for categorical variables. Results from cognitive testing are presented for each participant along with pertinent neonatal characteristics. These summaries are presented separately for those tested with MSEL and WISC-IV.

The mean overall score for each test (ELC for MSEL and FSIQ for WISC-IV) was compared to the expected norm of 100 using the one sample t-test. In addition, the one-sample t-test was used to compare subscale scores for the MSEL to the expected norm of 50 and subscale scores of the WISC-IV to the expected norm of 100. For both the MSEL and WISC-IV, an exact binomial test was used to assess whether the number of participants with a composite score more than 1 standard deviation below normal was greater than expected.

In both cross-sectional and longitudinal studies, testing is frequently performed with different instruments to accommodate age-appropriate testing. This creates challenges in interpreting neurocognitive test results when differing instruments are included. Both ELC and FSIQ measure overall cognitive status, based on a wide range of cognitive functions. Both tests are standardized to an age-appropriate population with an expected mean of 100 and standard deviation of 15. For analysis purposes, when using the overall measure of cognitive status obtained from both tests, we refer to the outcome as *Overall Cognitive Score (OCS)*. This approach has been used in studies that used different age-specific neurocognitive tests to assess the association between cognitive status and disease progression in children with HIV [22–24]. OCS scores were compared between age groups using the two sample t-test. In addition, using linear regression with OCS as the response variable, we performed a series of analyses to assess potential factors associated with neurocognitive outcome. Each characteristic was assessed separately using a model which included the testing instrument (MSEL or WISC-IV) as a covariate. Characteristics assessed included: sex; gestational age; weight at birth, 1 year and change from birth to 1 year; head circumference at birth, 1 year and change from birth to 1 year; duration of mechanical ventilation; admission preductal $PcCO_2$; POS; Brindle risk score; length of hospital stay; severity of CDH presentation (early presentation); position of the liver in the chest; and head ultrasound grading. Length of hospital stay was extremely prolonged in 2