Neurodevelopmental outcome in congenital diaphragmatic hernia: Evaluation, predictors and outcome

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Abstract
To review the reported neurodevelopmental outcome of congenital diaphragmatic hernia (CDH) survivors, identify important predictors of developmental disabilities, and describe the pathophysiological mechanisms contributing to adverse outcome. A Medline search was performed for English-language articles cross-referencing CDH with pertinent search terms. Retrospective, prospective, and longitudinal follow-up studies were examined. The reference lists of identified articles were also searched. Neurodevelopmental dysfunction has been recognized as one of most common comorbidity in congenital diaphragmatic hernia (CDH) and survivors. Disease severity impacts on neurological dysfunction. Neurodevelopmental follow-up in CDH children should become standard of care to improve neurological outcomes.

INTRODUCTION
Congenital diaphragmatic hernia (CDH) is a common anatomical anomaly in which there is herniation of the abdominal viscera into the thoracic cavity due to an incomplete closure of the pleuroperitoneal membrane. It is estimated to occur in approximately 1 in 2500 live births. Over the past several decades, the postnatal survival rate at tertiary centers has improved with reported rates of 70% to 90% [1,2]. Improved survival rates appear to be the result of advances in surgical technique, neonatal intensive care, extracorporeal membrane oxygenation (ECMO), and the widespread implementation of lung...
preservation ventilation strategies. While improving short-term morbidity and mortality are important goals, more recent research has focused on long-term outcome as equally important primary outcomes\textsuperscript{3-9}. Neurodevelopmental and neurofunctional impairments constitute one of the most common and most significant morbidity in CDH\textsuperscript{10}. There is an increasing concern for considerable delays in various neurological domains: cognitive, motor, language, and visuospatial skills, hearing impairment, and behavioral development\textsuperscript{5,10-16}.

The purpose of this review is to comprehensively examine the available literature that report on cognitive, motor, and behavioral development in these patients; to identify important predictors of developmental disabilities; and to summarize the pathophysiological mechanisms contributing to adverse outcome.

COMPREHENSIVE OUTCOME STUDIES

Short-term outcome (≤ 36 mo)

Several studies have evaluated the short-term outcome in CDH children and demonstrated that the neurodevelopmental deficits seen in CDH patients during infancy appears to be comparable to the data reported in infants born with other severe congenital malformation (e.g., congenital heart disease, giant omphalocele, bronchopulmonary dysplasia, preterm infants, and children with deletion 22q11 syndrome)\textsuperscript{17-21}. A study by Van Meurs et al\textsuperscript{22} showed that 25\% of CDH children that required ECMO had mild deficits, while seventeen percent showed significant delays. Comparable data were reported by D’Agostino et al\textsuperscript{23} showing average, mild delays and severe delays in 54\%, 25\% and 23\%, respectively. Bernbaum et al\textsuperscript{24} reported an increased incidence of periventricular leukomalacia and intraventricular hemorrhage (26\%), and seizure activity (5\%) in CDH survivors. More recently, Cortes et al\textsuperscript{25} assessed neurocognitive outcomes at 24 mo of age and showed that more than 50\% of CDH survivors demonstrated cognitive delays, while nearly 40\% were found to have neuromotor dysfunction. Chen et al\textsuperscript{26} evaluated motor skills in 13 CDH children during early childhood; nearly 80\% of participants showed impairments.

In a pilot study of 41 CDH patients enrolled in the Pulmonary Hypoplasia Program at the Children’s Hospital of Philadelphia, Danzer et al\textsuperscript{27} found a median of 2 years cognitive and language skills within the average, mild delays, and severe delays in 49\%, 36\%, and 15\% respectively. Motor skills were average in 46\% while 23\% had mild deficits, and 31\% had severe neuromotor deficits. Comparable data were recently reported by Wynn et al\textsuperscript{28} in a multicenter prospective follow-up study of 48 CDH survivors at 24 mo of age.

Intermediate-term outcome (37 mo to ≤ 5 years)

Neurological assessments during school age generally are relatively stable and more predictive of long-term outcome. However, data on preschool neurodevelopmental outcomes is sparse. Nijhuis-van der Sanden et al\textsuperscript{29} studied neuromotor skills in 32 CDH survivors. Thirty-eight percent had normal scores. A total of 34\% had mild delays and sixteen percent had significant problems\textsuperscript{30}. In a similar study, van der Cammen-van Zijlp et al\textsuperscript{31} found various degrees of neuromotor delays in 42\%.

In one of the largest prospective follow-up study, Danzer and associates\textsuperscript{32} followed 60 CDH patients. The majority of CDH children have more favorable neurodevelopmental outcome at early preschool age and performed well within the average range. Twenty-two percent of evaluated CDH patients had borderline scores. Eleven percent showed significant delays in at least one domain\textsuperscript{33}.

Long-term outcome (above 5 years of age)

As children get older, it is possible to assess and study a broader range of neurological function, however analogous to the data shown above, only a few reports focus on school age and adolescence outcome in CDH patients. Bouman et al\textsuperscript{34} studied 11 CDH patients at 10 years of age. Below average IQ scores were found in nearly half of the population. Jacobson et al\textsuperscript{35} compared 15 CDH survivors to age-matched controls at a follow-up of 13 years. Although the mean neurodevelopmental and functional scores were similar between groups, nearly one-fourth of the CDH children scored below average. Significant delays were found in 13\%.

Similarly, Rasheed et al\textsuperscript{36} reported the data of CDH survivors that required ECMO either after or before surgical closure of the diaphragm defect. IQ scores for children that had surgery before ECMO were within the average range, while children that underwent ECMO first had below average scores. Overall neurofunction scores were similar between groups.

Recently, Tureczek et al\textsuperscript{37} evaluated 33 CDH children without ECMO support at 9 years of age using the WPSSI-III and the Movement Assessment Battery for Children 2nd edition. Although they report that the overall neurocognitive scores were not significantly different than population norms, they reported increased rates of motor dysfunction\textsuperscript{38}.

The long-term implications of these findings throughout adulthood are uncertain. Continued outcome research is warranted as these children progress through school, since lower academic scores, learning disabilities, and/or the presence of behavioral problems, might be associated with increased risk of school failure which in turn may lead to poor social skills, low self-esteem, disinhibition, and delinquency. Of note, the improvements in perinatal care of CDH neonates in the past decade coupled with the improved understanding of the pathophysiological sequelae associated with CDH may make it difficult to extrapolate the reported data in currently school-age children to newborns born in the past decade. It is likely that current CDH survivors will have better neurological outcomes than those born just a generation or two before.
Longitudinal outcome
Similar to the lack of long-term outcome data, there is a paucity of longitudinal assessments. Longitudinal evaluations are important as it has been acknowledged that several neurodevelopmental disabilities may be transient, while others may continue to evolve later in life when more complex cognitive and executive performances are required.

To date, only three studies reporting on the longitudinal neurodevelopmental outcome in CDH. Gischler et al[31] evaluated 12 CDH infants every six months for the first two years of life. Cognitive and language scores at 6 and 24 mo were average. Neuromotor scores slightly improved from the low-average range to the average range.

Friedman et al[32] followed 23 CDH survivors during the first three years of life. Of the 17 children noted to have neurofunctional problems at three years of age, 13 had already variable degrees of neurofunctional impairments at one year.

In 2013, Danzer et al[12] longitudinally evaluated the neurodevelopmental outcome of 47 CDH children in the first three years of age. During the study period, BSID-III neurodevelopmental and motor scores improved in 19% and 37%, respectively. In spite of the performance improvements, the number of CDH patients with mild to severe delays in at least one neurodevelopmental area was greater than expected for the general population[10]. Seventy-two percent of the children scored within the average range for all three domains, while 17% were delayed in either neurodevelopmental or neurofunctional outcome, 11% had delays in all domains, and 6% remained severely delayed.

HEARING IMPAIRMENT
Hearing impairment, mainly sensorineural hearing loss (SNHL) can be viewed as another type of neurodevelopmental complication. SNHL appears to be a progressive phenomenon; with reported incidences between 0% to 100%[24,33-42]. In a recent report, Partridge and associates[33] followed 112 CDH patients. Interestingly, SNHL was found in approximately 3%, a rate comparable to the prevalence of SNHL in graduates from neonatal intensive care units for other problems (2%-6%). Unexpectedly, they found a high incidence (34%) of abnormalities in auditory brainstem response and/or behavioral audiometry consistent with conductive hearing loss.

Although hearing impairment in CDH has been attributed to a number of risk factors, the pathophysiology remains poorly understood. For example, need for ECMO, severe hypoxia, acidosis, duration of mechanical ventilation and NICU stay, and the prolonged exposure to ototoxic drugs have all been reported as risk factors[24,33-37]. Furthermore, genetic predisposition to hearing loss and cumulative noise exposure have also been postulated as potential causes of SNHL in CDH patients. Additional studies are necessary to define their role in the CDH population. In general, infants with hearing impairment are at increased risk for delayed language acquisition, poor social development, and impaired academic achievement. Early identification and appropriate intervention may be critical in minimizing adverse effects and optimizing developmental outcomes.

QUALITY OF LIFE
Although, quality of life (QoL) assessment has emerged as an essential outcome measurement in many high-risk patient populations (e.g., congenital heart disease, extremely low-birth weight children), few studies have evaluated QoL in the CDH population. Poley et al[34] studied 111 CDH children. Preschool CDH patients had lower scores in five of the thirteen domains tested. Adolescents demonstrated considerable deficits in several areas of every day functioning. No differences were found between young CDH adults and the control population.

In a study of 69 adults with CDH, Koivusalo et al[35] found lower QoL scores and the frequency of attaining higher educational levels (e.g., college) in 25% of the study population. Bouman et al[36] assessed the emotional outcomes and that 36% of CDH children may have depressive problems.

Chen et al[37] studied the QoL of 53 CDH children at a median age of 8 years and found that ongoing clinical problems translated into lower functional status, particularly in overall general health and interpersonal functioning. Further research is warranted to delineate associations between specific aspects of neurodevelopmental outcome and QoL, and to identify neurologic impairments that may be improved through early intervention. By characterizing the relationship between disease complexity, neurodevelopmental morbidity, and QoL, health care professionals and caregivers may be able to significantly improve the lives of CDH children and ensure their future success.

RISK FACTORS FOR ADVERSE NEUROLOGICAL OUTCOME
Based on the available outcome data, various risk factors for adverse neurodevelopmental sequelae have been identified[8,9,12,23-25,31,32,45]. For example, position of the liver one of the most important factors of survival. In one of the largest series of isolated left-sided CDH patients, Hedrick et al[1] demonstrated that neonates with intrathoracic liver position had a mortality of approximately 55% and 80% required ECMO. Of note, Danzer et al[38] reported that more than two-thirds of CDH children with prenatally diagnosed intrathoracic liver position had delayed neurodevelopmental function.

Several studies have reported a survival advantage of right-sided CDH compared to left-sided defects[46,47]. This improved survival of right CDH children must be cautioned by a high prevalence of associated problems, suggesting that the higher incidence of neurologic deficits these children may be in part due to the survival of
extremely sick right CDH patients.

The need for ECMO is associated higher risk of neurological impairments\[12,14,23,27-29,33,46,49\]. Whether the increased incidence of adverse outcome associated with ECMO indicates a more severe form of CDH or a reflection of ECMO-associated complications continues to be under discussion. In general ECMO is reserved for the sickest newborns\[50,51\]. ECMO therapy may also be linked to neurological impairments due to the need for anticoagulative therapy, development of intracranial hemorrhage, and alteration of intracranial blood flow secondary to the necessary ligation of the carotid artery. The type of ECMO modality used may impact function. Historically, venoarterial (VA) ECMO has been used. Recent studies suggest that venovenous ECMO may be as useful as VA ECMO with a lower prevalence of sequelae\[52,53\].

The need for a patch to repair the diaphragm or the need for oxygen beyond 30 d may also play an important role in neurological outcome\[17,21,24,46\].

In addition to the above mentioned potentially modifiable predictors, many independent risk factors of adverse neurodevelopmental outcome are not modifiable, such as innate patient-related variables, including associated malformations, genetic syndromes, the higher than expected incidence of autism and autism spectrum disorder\[54\]. The apparent link between CDH and autism spectrum risk is of concern. If more CDH children are diagnosed with autism in the future, one should consider including them as part of outcomes. Moreover, parental education and social-economic status, which are also not modifiable factors, are also associated with adverse outcome. Stolar et al\[55\] reported that low-level maternal education correlates with the incidence of delays. Wynn et al\[56\] expanded on these initial findings and showed that not only maternal education, but also paternal education and household income less than $30000 were associated with lower neurodevelopmental and functional scores.

**PATHOPHYSIOLOGIC MECHANISM**

While the abovementioned predictors support the concept that disease severity correlates with the severity of neurodevelopmental problems, the mechanisms remain poorly understood. Several reports suggest that children with CDH have a higher incidence of cerebral abnormalities than the general population\[55-57\]. Hunt et al\[58\] found a disturbingly high incidence of brain abnormalities in CDH newborns on postnatal magnetic resonance imaging studies. Danzer et al\[59\] found that the development of the brain in CDH neonates might be delayed. They also found that 18% of infants studied had periventricular leukomalacia, as well as delayed closure of the cerebral opercula in 14%. Although the etiology of central nervous system injury in CDH patients is almost certainly multifactorial, changes in cerebral circulation are common and appear to play a pivotal role\[55\]. In normal fetal brain development, the formation of the cerebral cortex begins at about 6 wk gestation with the formation of the ventricular zone of the dorsal and ventral germinal matrices, followed by a well-orchestrated sequence of structural changes including the gradual appearance of deep primary and more superficial secondary cortical infolding, neuronal migration and arborization, synaptogenesis, programmed cell death, oligodendrocyte maturation, and extensive reorganization of synaptic connections during the second half of gestation\[58,59\]. Beginning in the third trimester, myelination of the cerebral hemispheres accelerates\[60,61\]. These important processes during fetal brain development place an escalating demand on the cardiopulmonary system for delivery of oxygenated blood. The observed brain abnormalities in CDH might be in part caused by prolonged impairment of cerebral oxygen delivery. Of note, in children with congenital heart defects, the brain receives lower levels of oxygen-saturated blood from the right ventricle as a consequence of disordered fetal circulation\[62,63\]. In CDH fetuses, the left ventricle is one-third smaller and the left ventricular output is reduced\[60-64\]. These alterations may affect cerebral perfusion and compromise cerebral development. Of note, Buesing et al\[65\] showed that cerebral blood flow is altered in CDH survivors\[61,62\]. In addition to a prenatal insult, CDH neonates are exposed to the potential risk of hypoxia/ischemia, emboli, reactive oxygen species, acidosis, neuro-modulating drugs and inflammatory microvasculopathy before and after surgery, all of which may affect the white matter maturation and in turn neurodevelopment\[61,63,64,67\].

**CONCLUSION**

Infants and children with CDH often have significant neurodevelopmental and neurofunctional sequelae compared with population norms. Some of the identified early developmental abnormalities may improve over time. Identifying deficits early and providing early physical, occupational, and academic interventions may help to improve neurological morbidities before additional disabilities evolve and optimize long-term academic achievements. The American Academy of Pediatrics\[18\] has established follow-up guidelines for CDH survivors after discharge to highlight the importance of monitoring the developmental problems in this high-risk population throughout infancy and childhood.

Future research should focus on intervention strategies that not only reduce the pulmonary sequelae in CDH, but also in improving prenatal hemodynamics and cerebral blood flow to optimize brain development and improve outcome. Further, robust and longitudinal studies that incorporate advanced neuroimaging techniques and comprehensive assessments are warranted to further improve outcomes in CHD survivors.

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