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The prevalence of hearing loss in children with congenital diaphragmatic hernia: A longitudinal population-based study☆

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ABSTRACT

Background: The true prevalence of hearing loss among children with congenital diaphragmatic hernia (CDH) is unknown, with some studies reporting rates up to 60%.
Purpose: The purpose of this study was to determine the prevalence of hearing loss among children with CDH and compare it to age-matched controls.
Methods: We used population-based datasets to compare the number of hearing loss diagnoses in children younger than 10 years-of-age born between 1992 and 2009 with CDH to date-of-birth matched controls without CDH. Factors associated with CDH disease severity were analyzed to determine their effect on the prevalence of hearing loss. A sensitivity analysis was performed to determine if selection bias of improved care over the course of the study affected hearing loss in CDH patients. The prevalences of hearing loss were compared using Fisher's exact tests and statistical significance was defined as $p < 0.05$.
Results: A total of 529 children, 38 CDH cases and their 491 date-of-birth matched controls, met the inclusion criteria. Hearing loss was found in 7 children with CDH (18.4%) compared to 26 (5.3%) controls; the risk ratio (RR) of hearing loss was 3.48 (95%CI = 1.61–7.49, p = 0.006). There was no association between CDH disease severity and hearing loss.
Conclusions: CDH is associated with hearing loss compared to the general population. Our results suggest that congenital factors may contribute to hearing loss in CDH more than perinatal exposures.
Level of evidence: 3.

Bochdalek-type congenital diaphragmatic hernia (CDH) is an embryologic defect characterized by incomplete closure of the posterolateral diaphragm. CDH leads to herniation of abdominal organs into the thoracic cavity. The annual incidence of CDH is estimated to be 2.49–3.7 in every 10,000 live births [1–4]. CDH survivors may be affected by a number of comorbidities. These include pulmonary hypoplasia, abnormalities of pulmonary vasculature, gastroesophageal reflux, growth failure, chest wall and spinal deformities, cognitive delay and hearing loss [5–8]. The reported prevalence of hearing loss among CDH survivors varies widely, between 3.8% and 60% [9–11].

The cause of hearing loss in CDH patients remains uncertain and could be congenital or acquired [8]. Congenital hearing loss in CDH may be related to abnormal synchronous embryologic development of the cochlea and the diaphragm. Acquired hearing loss may be attributed to perinatal factors such as: hypoxia at birth, ototoxic drugs, hyperbilirubinemia, prolonged ventilation, high frequency oscillation ventilation, neuromuscular blockade, extracorporeal membrane oxygenation (ECMO), low birth weight, low APGAR scores, prolonged stay in a neonatal intensive care unit (NICU) or excessive noise in the NICU [10,12,13].

The aims of this case-controlled study were to determine the prevalence of hearing loss in children with CDH, to compare this prevalence to age-matched controls, and to determine if CDH disease severity is a predictor of hearing loss.

1. Methods

1.1. Patient selection

With ethics approval [HS20964 (H2017:252)], we used *Winnipeg's Surgical Database of Outcomes and Management* (WiSDOM) to identify all children with CDH born in the province of Manitoba between 1992 and 2009 for whom follow-up population-level data was available up

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to 10 years-of-age. WiSDOM is a database of clinical information for children with congenital surgical anomalies treated in Winnipeg since 1991. It includes demographic information, perinatal history, disease-specific information and intervention details. For CDH, the disease-specific details available are: defect side, defect size, presence of liver herniation, presence and severity of persistent pulmonary hypertension of the newborn and presence of a hernia sac.

Only patients with left and/or right, posterolateral CDH defects were included in this study. Defect size was described in accordance with the Congenital Diaphragmatic Hernia Registry [14]. A and B were classified as small, while C and D were classified as large. Severity of persistent pulmonary hypertension of the newborn was categorized as mild or severe by echocardiogram. The criteria for severe pulmonary hypertension were either bidirectional or right-to-left shunting through the patent ductus arteriosus or septal flattening.

We linked our clinical CDH data to the *Manitoba Center for Health Policy*. The *Manitoba Center for Health Policy* is a repository of population-level health, education and socioeconomic data for all individuals living in Manitoba [15]. Using *Personal Health Information Numbers* as unique identifiers, the WiSDOM data was submitted to *Manitoba Health*, an administrative agency responsible for public health care. The data was anonymized by scrambling the *Personal Health Information Numbers*. This is standard procedure for *Manitoba Center for Health Policy* linkage studies. *Manitoba Health* matched the CDH cases to controls from the general population using the *Manitoba Health Insurance Registry*. For each CDH patient 10 date-of-birth randomly matched controls were identified. Controls were drawn from the general population without discrimination by sex, gestational-age, birth weight, medical history or co-morbidities. Cases and controls without health care coverage for their first 10 years-of-life, due to death or emigration, were excluded. Perinatal characteristics of the entire cohort were collected from the *Hospital Abstracts* data set available in the *Manitoba Center for Health Policy*. These characteristics were birth weight, gestational age, sex, 1- and 5-min APGAR scores and length of hospital stay after birth.

1.2. Identifying hearing loss

Diagnoses of hearing loss were identified through *Medical Claims/Medical Services*, an administrative data set available through the *Manitoba Centre for Health Policy* that contains information about all compensation claims for medical services rendered in Manitoba. The *International Statistical Classification of Diseases 9th edition* (ICD-9) was used to identify individuals in our cohort diagnosed with unspecified hearing loss using codes starting with 389.

1.3. Statistical analysis

The linkage between WiSDOM and the *Manitoba Center for Health Policy* was done using SAS® statistical software, and the data analysis was performed using R® statistical software. The prevalence of hearing loss in CDH cases versus controls was compared using Fisher's exact tests. Statistical significance was defined as $p < 0.05$. The effect of disease severity was determined by logistic regression by considering clinical variables associated with worse outcomes: larger defect size, absence of hernia sac, liver herniation and severe pulmonary hypertension.

We performed a sensitivity analysis to determine if ascertainment bias influenced our primary analysis. As only survivors could be included, cases that may have had hearing loss had they survived were excluded. Because CDH survival has improved with time, we determined if the prevalence of hearing loss in the CDH cases born earlier differed from the prevalence in CDH cases born more recently.

2. Results

We identified 57 children with CDH diagnosed between 1992 and 2009, and 570 age-matched controls. After 19 CDH cases and 79 controls were excluded due to incomplete health care coverage for their first 10 years-of-life, the final CDH cohort consisted of 38 CDH cases and 491 CDH controls.

The perinatal characteristics are presented in Table 1 for the CDH and age-matched control individuals. CDH cases had significantly lower mean 1-min ($p < 0.001$) and mean 5-min ($p = 0.001$) Apgar scores. CDH cases had significantly longer hospital stays than controls ($p < 0.001$). There was no difference in birthweight ($p = 0.84$), gestational age ($p = 0.45$), or sex ($p = 0.94$) between the two groups. The disease-specific characteristics of the CDH patients are shown in Table 2. Logistic regression showed that these disease-specific characteristics associated with disease severity did not influence the occurrence of hearing loss.

Of the 38 CDH patients, 7 (18.4%) were diagnosed with hearing loss compared to 26 (5.3%) children in the age-matched control group (RR = 3.48, 95%CI = 1.61–7.49, $p = 0.006$) as shown in Table 1. The prevalence of hearing loss in CDH patients born between 1992 and 2000 was similar to the prevalence in CDH patients born between 2001 and 2009 (RR = 0.55, 95% CI = 0.14–2.11, $p = 0.425$). Because the number of CDH patients with hearing loss was less than or equal to 5 in each time period, the actual numbers are not published to protect patient confidentiality.

3. Discussion

We determined that the prevalence of hearing loss in children with CDH is 18.4%, greater than age-matched controls and has not changed over time. We found no correlation between variables associated with increased disease severity and the occurrence of hearing loss. These results suggest that a common pathology affecting the development of the diaphragm and auditory system may contribute more to hearing loss in CDH than perinatal interventions or exposures.

Previously published prevalence of hearing loss in CDH survivors ranges from 3.8% to 60% [9–11]. The range may be attributed to differing definitions of hearing loss, use of different diagnostic tools and variable lengths of follow-up. The real prevalence is likely greater than the reported low estimate, 3.8%, as this is less than the 5.6% observed in our control population.

Although cases and controls had similar gestational ages, birth weights and sex distribution, cases had lower Apgar scores and longer hospital admissions than controls. Many patients admitted to NICU have low Apgar scores and long admissions, but the prevalence of hearing loss in all NICU graduates is reportedly 3.2–10.2% [16,17]. Other risks factors for hearing loss include: ventilation for more than 5 days, asphyxia, prolonged use of aminoglycosides, supplemental oxygen or ECMO, family history of hearing loss, craniofacial deformity, genetic syndrome, birth weight less than 1500 g, low Apgar scores, sepsis, meningitis, cerebral infarction and hyperbilirubinemia [16–22]. CDH patients share many of these risks with other neonates requiring intensive care, yet the prevalence of hearing loss in CDH exceeds that expected for all NICU graduates. This suggests there may be an embryologic factor associated with the development of CDH that also influences the development of the auditory system. Understanding the complex embryology of the diaphragm and the inner ear continue inde-

Table 1
Characteristics of CDH cases (n = 38) and their age-matched controls (n = 491). The prevalence of hearing loss is significantly different between cases and controls.

	Cases (n = 38)	Controls (n = 491)	p Value
Birth weight (grams)	3488 (±467)	3467 (±587)	0.84
Gestational age (weeks)	39.33 (±1.17)	39.10 (±1.87)	0.45
Male (%)	21 (55.3)	261 (53.2)	0.94
1-min Apgar score	5.8 (±2.4)	8.0 (±1.6)	<0.001
5-min Apgar score	7.4 (±1.8)	8.4 (±2.1)	<0.007
Length of hospital stay (days)	25.0 (±26.3)	3.9 (±3.9)	<0.001
Hearing loss (%)	7 (18.4%)	26 (5.3%)	0.006

Table 2
CDH disease-specific characteristics.

	Cases (%)
Side of defect (n = 38)	
Left	33 (86.8%)
Defect size (n = 33)	
Small	26 (78.8%)
Large	7 (21.2%)
Presence of hernia sac (n = 37)	
Yes	8 (21.6%)
No	29 (78.4%)
Presence of liver herniation (n = 37)	
Yes	9 (24.3%)
No	28 (75.7%)
Persistent pulmonary hypertension of the newborn (n = 35)	
None	9 (25.7%)
Mild	14 (40%)
Severe	12 (34.3%)

pendently [23,24]; however, a common pathophysiologic mechanism may present itself in the future.

The number of syndromes presenting with both hearing loss and CDH - Pallister-Killian syndrome [25], Cornelia de Lange syndrome [26], chromosome 15q24 microdeletion syndrome [27], 22q11.2 deletion syndrome [28], Donnai-Barrow/facio-oculo-acoustico-renal syndrome [29], and Type 1 Simpson-Golabi-Behmel syndrome [30] - lends support to a common congenital etiology. However, the pathophysiology may not be as simple as congenital or acquired. One study found that although any degree of hearing loss was not associated with any post-natal risk factor, severe hearing loss was associated with ECMO, nonprimary hernia repair, prolonged ventilation and high furosemide exposure [8]. Perhaps fetuses with CDH are genetically predisposed to hearing loss, but CDH neonates exposed to one or more post-natal risk factors experience more severe hearing loss.

Post-natal risk factors for hearing loss in CDH survivors have been studied but no consensus has been reached. In a retrospective review of 16 CDH survivors, 4 of whom had sensorineural hearing loss, Masumoto et al. reported that prolonged use of pancuronium bromide, loop diuretics, mechanical ventilation and high-frequency oscillation ventilation might contribute to late onset of hearing loss [12]. However, Morini et al. did a multivariate analysis of variables independently found to be associated with hearing loss (lower gestational age, sepsis, older age at hearing test, more episodes of hypercapnia, increased use of inhaled nitric oxide, longer mechanical ventilation, longer aminoglycoside use, furosemide use, and pancuronium bromide) to find that only age at audiologic evaluation remained independently associated with hearing loss [10]. Furthermore, Robertson et al. found no difference in the prevalence of hearing loss between CDH patients treated with or without ECMO [11]. And, ECMO was not a risk factor for hearing loss in Dennett et al.'s study of 122 CDH patients but cumulative aminoglycoside treatment was a risk [31].

The general improvement of neonatal care over time, including the use of gentle ventilation and improved monitoring may play a role in the improved outcomes for CDH children [32,33]. To determine if our CDH cohort was biased as only survivors were eligible for assessment, we performed a sensitivity analysis. When we separated our CDH cohort in two groups by year of birth, 1992–2000 and 2001–2009, we found no difference in the prevalence of hearing loss. This further supports the theory that hearing loss in CDH is not indicative of treatment, but that the two defects are inherently associated.

We acknowledge several limitations of this study. First, this study is limited by its retrospective nature. Second, we were unable to differentiate between conductive, sensorineural or mixed hearing loss, and we could not determine the severity of hearing loss. Third, because the administrative dataset used to select controls did not contain birth characteristics we could only match cases and controls by date of birth. Finally, clinic variables for analysis were limited to those recorded in the WiSDOM database; notably unavailable data were use of ototoxic drugs, type and duration of ventilation and hypoxic episodes. ECMO was not used for CDH patients in our study. Despite these limitations, our study is unique because we used population-level administrative data to compare CDH patients to controls.

4. Conclusion

This study demonstrates that children with CDH are at increased risk of hearing loss compared to the general population. Furthermore, congenital factors may contribute more to this hearing loss than perinatal exposure to risk factors alone since the prevalence of hearing loss in other NICU graduates is not as high.

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The output of data used for this paper was generated using SAS software, Version 9.4 of the SAS system for Unix, Copyright © 2016 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

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