Wednesday 27th April 14.00 – 15.00
Live Abstract Presentations (with recording) in Main Auditorium

24 Syndromic CDH: current incidence and outcome. Analysis from the CDHSG Registry data

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52 LONP1 is a novel gene causing congenital diaphragmatic hernia with primary effects on lung development and mortality

Lu Qiao[1,2], Le Xu[3], Lan Yu[1], Julia Wynn[1], Rebecca Hernan[1], Xueya Zhou[1,2], Christiana Farkouh-Karoleski[1], Usha S Krishnan[1], Julie Khlevner[1], Aliva De[1], Annette Zygmunt[1], Timothy Crombleholme[4], Foong-Yen Lim[5], Howard Needelman[6], Robert A Cusick[6], George B Mychaliska[7], Brad W Warner[8], Amy J Wagner[9], Melissa E Danko[10], Dai Chung[10], Douglas Potoka[11], Przemyslaw Kosiński[12], David J McCulley[3], Mahmoud Elfiky[13], Kenneth Azarow[14], Elizabeth Fialkowski[14], David Schindel[15], Samuel Z Soffer[16], Jill M Zalieckas[17], Badri N Vardarajan[18], Gudrun Aspelund[1], Vincent P Duron[1], Frances A High[17,19,20], Xin Sun[3], Patricia K Donahoe[19,21], Yufeng Shen[2,22,23], MD and PHD Wendy Chung, Wendy K Chung[1,24], Ms Rebecca Hernan, Rebecca Hernan
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77 ROLE OF MAJOR CARDIAC ABNORMALITIES IN HIGH-RISK CONGENITAL DIAPHRAGMATIC HERNIA INFANTS

MD Laura Valfre[1], MD Andrea Conforti[1], MD Irma Capolupo[1], MD Alessandra Toscano[1], MD Alessandra Di Pede[1], MD Annabella Braguglia[1], Prof Pietro Bagolan[1,2]
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99 The Role of Endothelial to Mesenchymal Transition in Congenital Diaphragmatic Hernia Pulmonary Hypertension

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106 Brain development is altered in fetuses with congenital diaphragmatic hernia in the rabbit model

Dr Lennart Van Der Veeken[1,2], Dr. Francesca Russo[1], Dr. Tom Bleeser[1], Dr. David Basurto[3], Mr. Yannick Regin[3], Dr. Doaa Emam[4], Dr. Willy Gsell[3], Prof. Uwe Himmelreich[3], Prof. Steffen Rex[1], Prof. Jan Deprest[1]
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24

Syndromic CDH: current incidence and outcome. Analysis from the CDHSG Registry data

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Background: Congenital Diaphragmatic Hernia (CDH) associated with genetic syndromes are rare. The aim of this study was to describe the incidence of these associations and the postnatal outcomes from a large database for CDH.

Methods: Data from the multicenter, multinational database on infants with CDH (CDHSG Registry) born from 1996 to 2020 were analyzed.

Results: A total of 12 553 patients were entered in the registry during the study period, and 416 had associated syndromes, representing 3.3% of all CDH cases in the registry. The overall survival to discharge for syndromic CDH was 33%. A total of 53 different associated syndromes were reported.

The most common were Fryns Syndrome (19,9% of all syndromes, 16,9% survival), Trisomy 18 or Edward´s syndrome (17,3%, 8% survival), Trisomy 21or Down Syndrome (9,1%, 47% survival), Trisomy 13 or Pataus Syndrome (6,7%,14% survival), Cornelia de Lange (6,5 % of all syndromes, 22% survival), Pallister-Killian (5,5 % of all syndromes, 39,1% survival) and Dandy-Walker malformation (4,6% of all syndromes, 36,8% survival).

The syndromic CDH group had lower birth weight and gestational age at birth, and increased incidence of bilateral CDH (2,9%) and rates of non-repairs (53%). The length of hospital stay was longer, as was the need for O2 at 30 days. ECMO was used only in 18% of the cases. Other associated anomalies were more common in syndromic CDH.

Conclusion: Syndromic CDH is rare, only 3,3% and survival rates are low. Given higher rates of non-repair and decreased ECLS use, along with a high early mortality, decision-making regarding goals of care clearly influence outcome. Survival varies depending on the genetic cause. When these patients survive the first week, survival to discharge is possible. Early molecular diagnostics may influence the decision making.

52

LONP1 is a novel gene causing congenital diaphragmatic hernia with primary effects on lung development and mortality

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Background: Although the role of genetics in congenital diaphragmatic hernia (CDH) has been established, our understanding of the genetic basis is incomplete.

Methods: To investigate further the genetics of CDH, we analyzed de novo coding variants in 827 proband-parent trios using whole genome sequencing.

Results: We identified an overall significant enrichment of damaging de novo variants, especially in constrained genes. We identified LONP1 (Lon Peptidase 1, Mitochondrial) as the most common genetic cause of CDH in 3% of cases due to both de novo and inherited variants. The LONP1 segregated with CDH in familial cases. Cases with CDH mutation had higher mortality and more frequently required extracorporeal membrane oxygenation. Mice with lung epithelium specific deletion of Lonp1 but an intact diaphragm die immediately after birth with severe reduction of lung growth, suggesting the LONP1 has a primary effect on lung development independent on the effect of compression of the lungs in utero during fetal development.

Conclusion: Our findings suggest that some CDH genes also have primary effects on lung development and could explain some of the variability observed in lung and pulmonary vascular outcomes in patients.

77

ROLE OF MAJOR CARDIAC ABNORMALITIES IN HIGH-RISK CONGENITAL DIAPHRAGMATIC HERNIA INFANTS

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Introduction
Congenital diaphragmatic hernia (CDH) is a severe congenital anomaly with high mortality rate, commonly reported to be secondary to pulmonary hypertension. Although risk factors in CDH infants were extensively investigated, less reported was the impact of major cardiac anomalies (CHD) on severity and mortality. Aim of the present study was to evaluate postnatal outcomes in a cohort of high-risk CDH infants, on regards of CHD.
Methods
A prospective collected database (2006-2019) of high-risk CDH infants (prenatally diagnosed and/or respiratory symptoms within 6 hours) was searched and patients classified based on CHD presence/absence. Demographic, clinical presentation and mortality were evaluated.
Results
During the study period, 239 CDH infants were treated. Table summarized main results
Conclusion
CHD infants experienced more severe diaphragmatic defects, liver up, more patch repair, less cdh repair, higher rate of pulmonary hypertension, and increased mortality. Further studies are needed to better understand the extent of CHD inference in CDH patients.

Images

	CHD + 33 patients (14)	CHD - 206 patients (86)	p
GA week; median IQR	37 (37-38)	38 (37-39)	0.001
Birth weight gr; median IQR	2490 (1950-3068)	2933 (2600-3300)	0.005
Left Side (%)	27 (82)	177 (86)	0.59
Liver up (%)	20 (60)	90 (44)	0.005
Surgery (%)	14 (42)	149 (72)	0.001
Patch	9/14 (64)	47/149 (32)	0.01
Cardiac Surgery	5 (15)	0	0.01
Pulmonary hypertension (%)	28 (85)	93 (45)	<0.0001
Other anomalies (%)	3 (9)	18 (9)	1
Sepsis (%)	11 (33)	56 (27)	0.5
Pleural effusion (%)	10 (30)	62 (30)	1
Mortality (%)	23 (70)	63 (31)	<0,0001

99

The Role of Endothelial to Mesenchymal Transition in Congenital Diaphragmatic Hernia Pulmonary Hypertension

Jamie Gilley[1], Hui Li[1], Yinka Olutoye, II[1], Walker Short[1], Sundeep Keswani[1]
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Background: Pulmonary hypertension (PH) is a significant contributor to morbidity and mortality in congenital diaphragmatic hernia (CDH). CDH pulmonary arteries have reduced intraluminal diameter and altered flow patterns due to vascular extracellular matrix (ECM) remodeling. Endothelial-to-mesenchymal transition (EndoMT) has been implicated in the pathogenesis of ECM deposition in pediatric and adult PH diseases but has not been evaluated in CDH-PH. A hallmark of EndoMT is loss of CD31 expression by endothelial cells and upregulated mesenchymal markers such as α-SMA and type I collagen. We hypothesize that endothelial cells from CDH patients are more susceptible to EndoMT and that EndoMT is contributing to the pathologic vascular remodeling seen in CDH-PH.

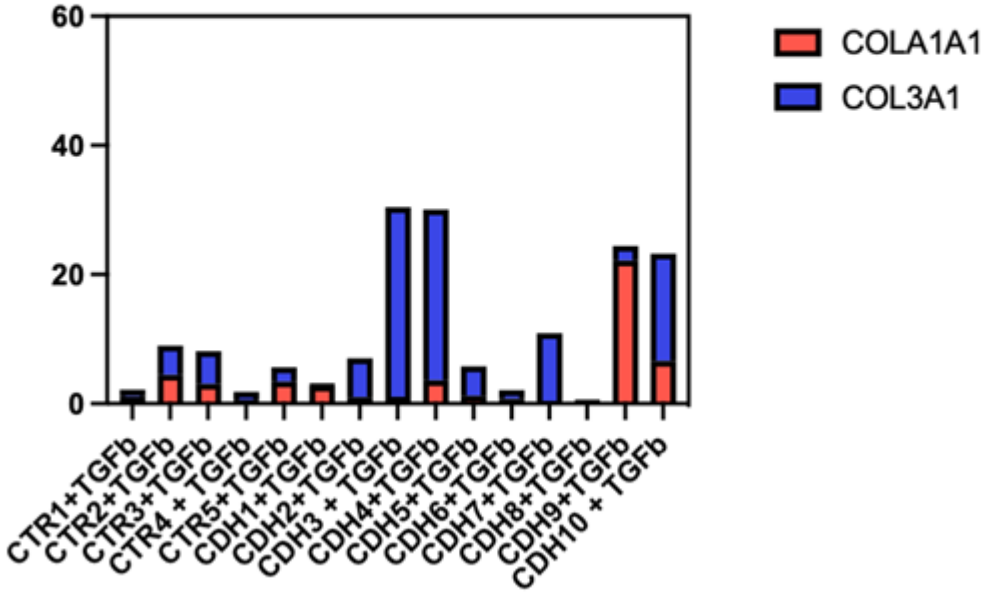
Methods: Endothelial cells were isolated from human umbilical veins (HUVECs) obtained at birth from CDH (n=10) and healthy control (n=5) patients with post-natal clinical outcomes assessed. A RT-qPCR profiler array including 38 EndoMT markers was performed on RNA from HUVEC samples following 24 hours of TGFB exposure. Pulmonary arteries of deceased CDH patients from our biobank were dissected with laser capture microdissection (LCM) and sent for proteomic profiling to detect proteins associated with EndoMT (n=3 CDH).

Results: RT-qPCR revealed elevation of EndoMT markers COL1A1 and COL3A1 in CDH HUVECs when compared to controls (Figure 1). CDH infants with elevated collagen levels were noted to have worse clinical manifestations of PH noted by need for extracorporeal membrane oxygenation and PH therapies when compared to CDH samples with less severe PH. Proteomic profiling of LCM-dissected vessels from human CDH lung tissue robustly detected fifty-three proteins associated with ECM pathways.

Conclusions: Our results reveal that infants with CDH have increased expression of biomarkers associated with increased EndoMT in both lung tissue and HUVEC samples. The results of our study also suggest that EndoMT may contribute to the pathologic vascular ECM remodeling leading to CDH-PH.

Graph

Figure 1:


60
40
20
0
COLA1A1
COL3A1
CTR1+TGFb
CTR2+TGFb
CTR3+TGFb
CTR4 + TGFb
CTR5+TGFb
CDH1+TGFb
CDH2+TGFb
CDH3 + TGFb
CDH4+TGFb
CDH5+TGFb
CDH6+TGFb
CDH7+TGFb
CDH8+TGFb
CDH9+TGFb
CDH10 + TGFb

106

Brain development is altered in fetuses with congenital diaphragmatic hernia in the rabbit model

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Introduction
Children with congenital diaphragmatic hernia (CDH) are at risk for neurodevelopmental delay. It is unknown if brain development is already disturbed prenatally. Herein, we examined brain development in fetal rabbits with surgically created DH.
Methods
Two cornual-end fetuses underwent surgical DH creation on day 23 (term=d31). DH-pups and littermate controls were harvested at term. Ten randomly chosen DH-pups and 11 controls underwent transcardial perfusion for brain fixation and measurement of brain volume, brain folding, neuron and synaptic density, pre-oligodendrocyte count, proliferation and vascularization. Twelve other DH and 11 controls had echocardiographic assessment of cardiac output and aortic and cerebral blood flow, Magnetic Resonance Imaging (9.4T) for cerebral volumetry, and molecular assessment of (neo-) vascularization markers.
Results
DH-pups had lower lung-to-body weight ratio (1.3±0.3 vs 2.4±0.3%; p<0.0001) and lower heart-to-body weight ratio (0.007±0.001 vs 0.009±0.001; p=0.0006) but comparable body weight and brain-to-body weight ratio. DH-pups had a lower left ventricular ejection fraction, aortic and middle cerebral artery blood flow (39±8 vs 54±15mm/beat; p=0.03) as compared to controls but left cardiac ventricular morphology was comparable. Fetal DH-brains were similar in volume but the cerebellum was less folded (perimeter/surface area: 25.5±1.5 vs 26.8±1.2; p=0.049). Furthermore, DH brains had a thinner cortex (143±9 vs 156±13µm; p=0.02). Neuron densities in the white matter were higher in DH fetuses (124±18 vs 104±14; p=0.01), with comparable proliferation rate. Pre-oligodendrocyte count was lower, coinciding with lower endothelial cell count.
Conclusion
In fetal rabbits with surgically induced DH, brain development is altered. In DH, brains were less folded and had a higher neuron density compared to controls. This coincided with a lower left cardiac output and a lower aortic and middle cerebral artery blood flow. Furthermore, the density of endothelial cell in DH brains was lower. These results indicate that in CDH, brain development is already altered prenatally.

Images

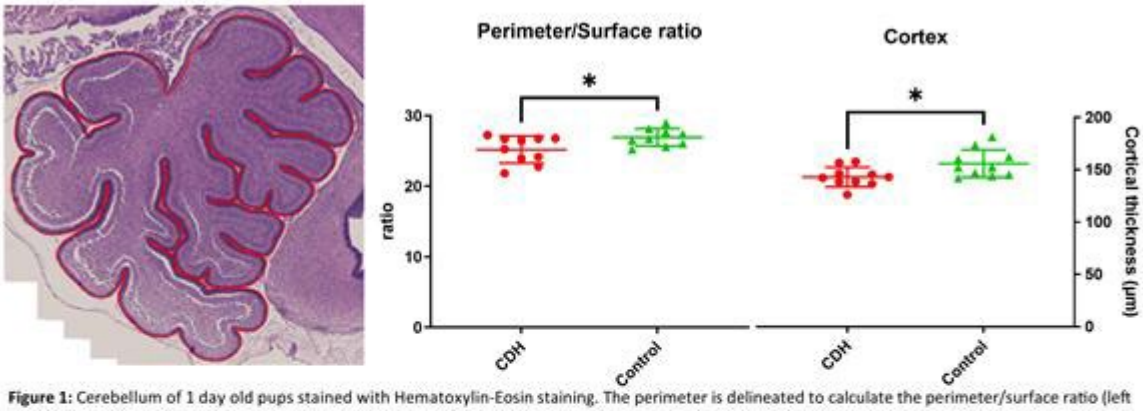

Figure 1: Cerebellum of 1 day old pups stained with Hematoxylin-Eosin staining. The perimeter is delineated to calculate the perimeter/surface ratio (left graph). Secondly, the cortical thickness is measured (right graph). * indicates $p<0.05$