Congenital Diaphragmatic Hernia

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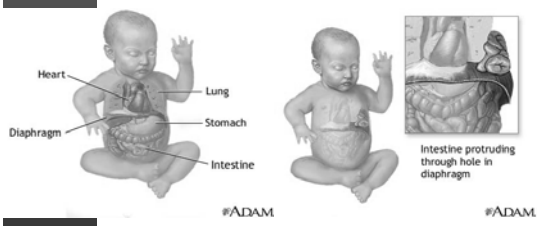
Congenital Diaphragmatic Hernia



Congenital Diaphragmatic Hernia

- *1679, Lazarus Riverius* 1st described CDH
  - He noted CDH during a postmortem examination of a 24-year-old person
- *1701, Sir Charles Holt* described the classical clinical & postmortem findings of an infant with CDH

Congenital Diaphragmatic Hernia

- *1761, Giovanni Battista Morgagni* published review of CDH, describing the classic anterior diaphragmatic hernia, now named the *Morgagni hernia*
- *1848, Victor Alexander Bochdalek*, described both right & left posterolateral CDH, called the *Bochdalek hernia*
- *1946, Gross* reported the 1st successful repair of a neonate with CDH within the 1st 24hrs

Congenital Diaphragmatic Defects

- Bochdalek – 90% of cases
- Morgagni – 5-10% of cases
- Hiatus hernia - rare

Congenital Diaphragmatic Hernia

- Bochdalek hernia –
  - Posterolateral defect
    - Failure of the pleuroperitoneal folds to develop
    - Improper or absent migration of the diaphragmatic musculature
  - Occurs approximately 6 weeks of gestation
  - *left sided* Bochdalek seen in 90% of all cases
  - Bilateral lesions are rare

Congenital Diaphragmatic Hernia

- Morgagnii Hernia -
  - Anterior midline
    - Through the sternocostal hiatus of the diaphragm
  - Represents 5-10% of all cases
  - 90% *right sided*
- Hiatus Hernia
  - Rare in newborns
  - Hernia of stomach occurs through the esophageal hiatus

Congenital Diaphragmatic Hernia

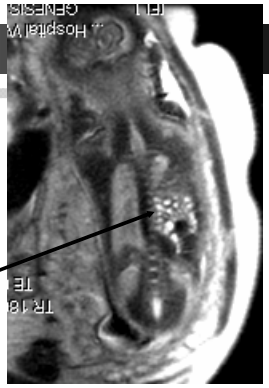
- Prenatal diagnosis
  - 50% diagnosed early in pregnancy
  - Week 16 and 24
    - At first routine ultrasound
    - If polyhydramnios noted
  - Right sided more difficult to diagnose
  - Findings:
    - Stomach or bowel in left chest - level with the 4 chambered view of the heart
    - Mediastinal shift away from the side of the lesion

Congenital Diaphragmatic Hernia

Prenatal Diagnosis

- Ultrasound -
  - usually done as routine study or if polyhydramnios noted
- CT/MRI –
  - best to differentiate difficult cases
  - allows prognostic measurements to be taken

MRI Scan on CDH Patient



Congenital Diaphragmatic Hernia

- **Prenatal Factors – prognostic indicators**
  - **Early diagnosis, <25 weeks**
  - **Polyhydramnios**
  - **Intrathoracic stomach bubble**

Initially thought to predict high mortality, but none have been found to be consistently reliable

Congenital Diaphragmatic Hernia

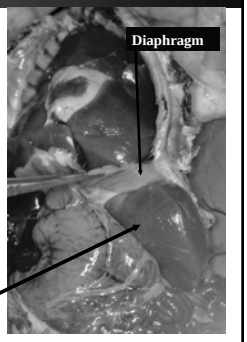
- **Prenatal Factors – prognostic indicators**
  - **Right lung diameter to head circumference, known as lung:head ratio**
  - **<0.6 correlated with 100% mortality**
  - **Those in mid-range, less predictive**
  - **LHR combine with liver in chest used by fetal surgery centers to predict high mortality**

Extreme measures appear helpful, but when tested in a prospective randomized trial for fetal surgery, LHR in the mid-ranges were not predictive of mortality

Harrison, et al., NEJM, Vol 349, 2003

Fetal Surgery

- **Initial repair of CDH in utero showed no improved outcome**
- **Focus on lung growth in utero – tracheal ligation (***Wilson, J with permission***)**



Harrison, et al., NEJM, Vol 349, 2003

Table 2. **Pregnancy Outcomes and Complications According to the Actual Treatment.***

Outcome or Complication	Standard Care (N=13)	Tracheal Occlusion (N=11)	P Value
Maternal death — no. (%)	0	0	
Maternal blood transfusion — no. (%)	0	0	
Maternal infection (wound) — no. (%)	0	1 (9)	
Preterm labor — no. (%)	4 (31)	8 (73)	0.10
PROM — no. (%)	3 (23)	11 (100)	<0.001
Time from tracheal occlusion to PROM — days			
Mean		24.8±14.8	
Range		5–52	
Time from PROM to delivery — days			
Mean	<1	9.5±8.5	
Range		0–28	
Placental abruption — no. (%)	1 (8)	3 (27)	0.30
Mode of delivery — no. (%)			
Planned EXIT		11 (100)	
Induced vaginal delivery	12 (92)	0	
Cesarean delivery	1 (8)	0	
Gestational age at delivery — wk			<0.001
Mean	37.0±1.5	30.8±2.0	
Range	34.0–39.0	28.0–34.0	
Birth weight — kg	3.03±0.48	1.49±0.36	<0.001

* Plus–minus values are means ±SD. PROM denotes premature rupture of the membranes, and EXIT ex utero intrapartum therapy.

Harrison, et al., NEJM, Vol 349, 2003

Table 3. **Ninety-Day Survival According to Assigned and Actual Treatment and According to the Lung-to-Head Ratio.**

Group		Lung-to-Head Ratio		Total
	≤0.78	0.79–1.06	1.07–1.39	
	number/total number (percent)			
Assigned treatment				
Standard care	0/0	6/9 (67)	2/2 (100)	8/11 (73)
Tracheal occlusion	0/1	7/9 (78)	3/3 (100)	10/13 (77)
Actual treatment				
Standard care	0/0	8/11 (73)	2/2 (100)	10/13 (77)
Tracheal occlusion	0/1	5/7 (71)	3/3 (100)	8/11 (73)
Total	0/1	13/18 (72)	5/5 (100)*	18/24 (75)

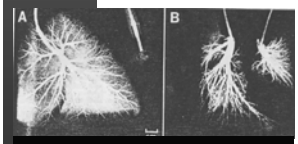
* P=0.04 for a trend of increased survival with a higher lung-to-head ratio (non-parametric test for trend).

Congenital Diaphragmatic Hernia

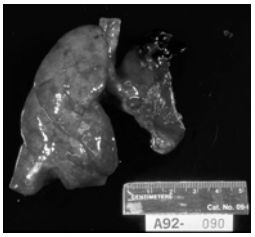
- Mortality related to
  - Pulmonary hypoplasia
  - Persistent Pulmonary Hypertension
  - Associated Anomalies
    - Fryns syndrome
    - Trisomy 13 & 18
    - De Lange syndrome
    - Cardiac

Congenital Diaphragmatic Hernia

- **Lung hypoplasia**
  - **Bilateral hypoplasia**
  - **More severe on the side of the hernia**



A. Normal Lung; B. Left CDH



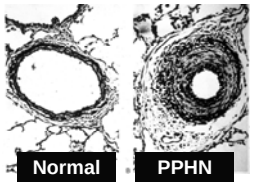
PRENATAL DIAGNOSIS OF CDH: HOW SHOULD THE PATIENTS BE DELIVERED?

B Frenckner , et al, CDH Registry, Abstract, ECMO Symposium 2005

- N=848, survival 66% (363/848)
  - C/S survival 70%
  - Induced vaginal delivery, 67%
  - Spontaneous vaginal delivery, 62%

Congenital Diaphragmatic Hernia

- Pulmonary hypertension
  - Anatomic – medial artery hyperplasia
  - Functional, secondary to hypoxia, acidosis

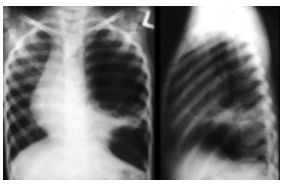


Congenital Diaphragmatic Hernia

- Differential diagnosis
  - Bronchogenic cyst
  - Cystic adenomatoid malformation
  - Congenital lobar emphysema
  - Pneumothorax
- Prenatal diagnosis
  - CT &/or MRI important to help differentiate these lesions

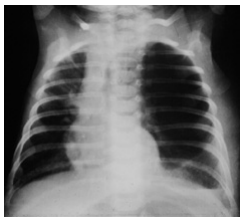
Congenital Diaphragmatic Hernia

- Cystic adenomatoid malformation
  - Can see shift of mediastinum
  - Intestinal contents normal position



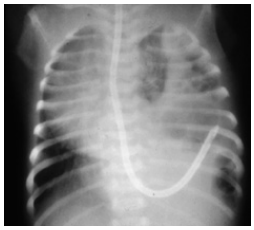
Congenital Diaphragmatic Hernia

- Congenital lobar emphysema
  - Usually only one cyst, not multiple
  - Intestinal contents normally located



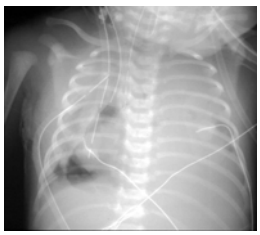
Congenital Diaphragmatic Hernia

- Congenital diaphragmatic hernia
  - Intestinal contents in chest
  - Shifted mediastinum
  - Multiple cystic lesions
  - Stomach may be in chest
  - Liver &/or spleen may be in chest



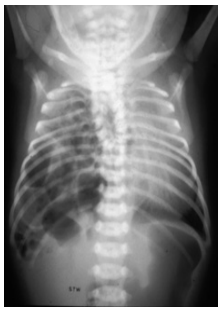
Congenital Diaphragmatic Hernia

- Diagnosis can be difficult at birth if patient is intubated immediately in delivery room prior to ventilation
  - NG tube indicating stomach in chest
  - May need UGI



Congenital Diaphragmatic Hernia

- Right Sided hernia more difficult to diagnose
  - Stomach may not be in the defect
  - Liver may be in the chest
  - Mediastinal shift may not be as pronounced



Congenital Diaphragmatic Hernia

- Idiopathic birth malformation
  - Majority sporadic
  - 2% familial association
- Occurrence, 1:2000-4000 births
- Represents 8% of all major congenital anomalies
- 30-50% incidence of other malformations associated with CDH
  - Cardiovascular
  - Genitourinary
  - Gastrointestinal
  - Lethal anomalies in 16%

Genetics of CDH

- Questions –
  - Is CDH the result of malformed diaphragm during development, resulting in hypoplastic lungs?
  - Is CDH the result of malformed lung, and resultant malformed diaphragm during development ?
  - Is CDH multiple causes ?

Smith, et al., Paediatric Respiratory Reviews, Vol 3, 2002

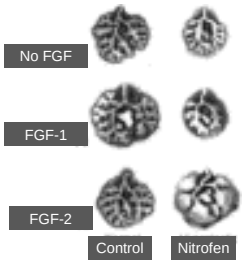
Genetics of CDH

- Fetal models of CDH using chemicals to induce the lesion:
  - Nitrofen given to rats at specific points in gestation produce CDH
    - Disruption of airway branching correlates with & precedes CDH
    - Indicates an intrinsic defect of lung development in CDH in this model

Jesudason EC, et al., J Pediatric Surgery, Vol. 35, pp 124-127, 2000

CDH: Pathophysiologic Mechanisms

- Fibroblast growth factor (FGF) are known to facilitate mammalian lung development
  - Appears to be important in airway branching
  - Lungs of rats treated with nitrofen do not respond to stimulation by FGF



Jesudason EC, et al., J Pediatric Surgery, Vol. 35, pp 914-922, 2000

"the Chicken or the Egg?"

Abnormal Lung Development

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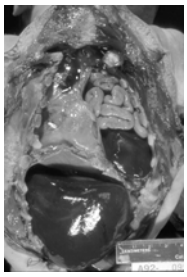
Abnormal Diaphragm Development



CDH: Pathophysiologic Mechanisms

- Vitamin A
  - Important in lung development
  - Wilson, et. al, noted high incidence of CDH in pups of Vit A deficient rats
  - Human infants with CDH have significantly reduced levels of retinol & retinol-binding protein
  - Transgenic mice in which both copies of the retinoic acid receptor (Vit A receptor) gene have been deleted display CDH with left lung agenesis & lung hypoplasia
  - Thebaud, et. al, have shown reduction of CDH in the nitrofen model with prenatal treatment with Vitamin A

CDH: Pathophysiologic Mechanisms

- Surfactant
  - Studies in animals models have shown CDH animals to be surfactant deficient
  - Nitrofen model
    - Surfactant phospholipids & SP-A decreased, but capacity to produce surfactant was equal to controls
  - Human data less clear
  - No improved outcome in human multi-centered controlled trials with surfactant use in the CDH patient

CDH: Pathophysiologic Mechanisms

- Glucocorticoids
  - Animal models indicate decreased levels of saturated phosphatidylcholine, total lung DNA & total lung protein, indicating lung immaturity
  - Question – would antenatal glucocorticoids improve outcome ?
    - No human data to support this use

Congenital Diaphragmatic Hernia

- Treatment
  - Conventional ventilation
  - HFOV
  - Inhaled nitric oxide
  - Permissive hypercapnia
  - Surfactant
  - ECMO
  - Liquid ventilation

Congenital Diaphragmatic Hernia

- Ventilation strategies
  - Reduce ventilator-induced lung injury
  - Pressure limited ventilation
  - Tolerance of higher $PaCO_2$
  - Avoidance of paralysis, use sedation

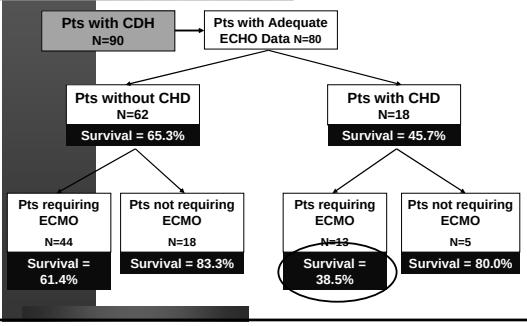
Permissive Hypercapnia

Stolar, reported 84% survival to discharge in 120 infants treated with this method

Boloker, et al., J of Ped Surg, Vol 37, 2002

CDH Outcome – Congenital Heart Disease

CNMC Data: 1990- 2000



Congenital Diaphragmatic Hernia

- High Frequency Ventilation - HFOV
  - Results from HIFI study group in the US & studies by Paranka et al., did not show benefit
  - Reyes, et al., Somaschini, et al., & Cacciari, et al., have shown early use of HFOV can improve outcome

Paranka, et al., Pediatrics, Vol 95, 1995
HIFI study group, NEJM, Vol 320, 1989
Reyes, et al., J Pediatric Surgery, Vol 33, 1998
Somaschini, et al., Eur J Pediatrics, Vol 158, 1999
Cacciari, et al., Eur J Pediatric Surgery, Vol 11, 2001

Congenital Diaphragmatic Hernia

- Inhaled nitric oxide
  - Multi-center NIH trial did not show long-term improvement in outcome with use of iNO
  - Meta-analysis and Cochrane review showed no improved outcome in the CDH population
  - May be some evidence for use post-ECMO

The Neonatal Inhaled Nitric Oxide Study Group (NINOS), Pediatrics, Vol 99, 1997
Finer, NN, Cochrane Database Syst Rev, Vol 4, 2001

Congenital Diaphragmatic Hernia

- Surfactant
  - Animal data to support deficiency
  - Human data is not conclusive
  - Lotze, et al, conducted prospective multi-center randomized trial – no effect on outcome

Lotze, et al., J Pediatric Surgery , Vol 29, 1994

Congenital Diaphragmatic Hernia

- Liquid Ventilation
  - Use of fluorocarbons to provide gas delivery & removal of CO_2
  - May be a useful method of stimulating lung growth through distention of lung
  - Requires further study

Major, et al., J Pediatric Surgery, Vol 30, 1995

Pranikoff, et al, J Pediatric Surgery, Vol 31, 1996

Congenital Diaphragmatic Hernia

- ECMO
  - Data from the ECLS registry shows that survival has remained the same over the years, 50-60%
  - UK ECMO trial failed to support ECMO use in CDH, but very stringent entry criteria (OI>60)
  - Cochrane review showed significant survival for all infants, including CDH

UK Collaborative ECMO Trial, Lancet, Vol 348, 1996

Elboume, et al., Cochrane Database Syst. Rev., CD001340, 2002

Congenital Diaphragmatic Hernia

Treatment	Prospective Randomized Controlled Trial	Effective Therapy
HFOV	Yes	No
iNO	Yes	No
Permissive Hypercapnia	No	-
Surfactant	Yes	No
ECMO	Yes?	No/Yes
Liquid Ventilation	No	-

Congenital Diaphragmatic Hernia

- Conclusions:
  - Cause is still unknown, probably multifactorial
  - Diagnosis prenatally should be improved with routine ultrasound and follow-up studies with CT/MRI
  - Fetal surgery has not been found to improve outcome
  - Treatment is still controversial