# LIMB BODY WALL COMPLEX: DEFINITION, MULTI-DISCIPLINARY REVIEW OF CASES AND DISCUSSION OF ETIOPATHOGENESIS

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*March 16, 2018*

*Paris, France*

# INTRODUCTION

## Limb Body Wall Complex – Definition:

American Journal of Medical Genetics 28:529–548 (1987)

**Limb Body Wall Complex:** I. Pathogenesis

**M.I. Van Allen, C. Curry, and L. Gallagher**

*Department of Medicine, University of Washington, Seattle (M.I.V.A., L.G.) and Department of Pediatrics, Valley Children's Hospital, Fresno, California (C.C.)*

"The diagnosis was based on the presence of two out of three of the following: exencephaly or encephalocele with facial clefts; thoraco- and/or abdominoschisis; and limb defects."

# INTRODUCTION

## Limb Body Wall Complex – Etiopathogenesis:

**Streeter *et al*, 1930**

- **Anomalies of the early embryonic disc (ectodermal placodes)**

**Torpin *et al*, 1965**

- **Amniotic rupture, disruption**

**Van Allen *et al*, 1987**

- **Vascular hypoperfusion**

**Craven *et al*, 1997**

- **Failure of amniotic fusion**

**Hunter *et al*, 2011**

- **Primary ectodermal failure in the early embryonic disc**

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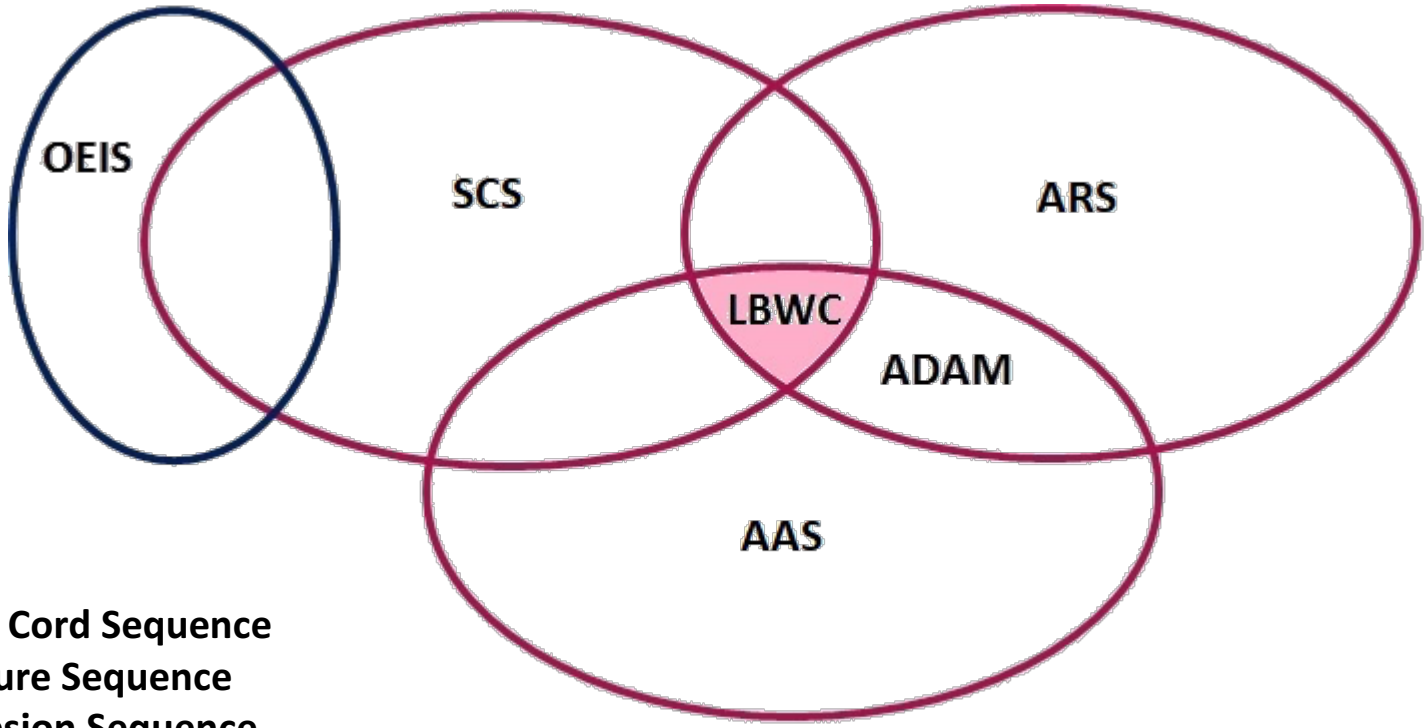


**SCS: Short umbilical Cord Sequence**
**ARS: Amniotic Rupture Sequence**
**AAS: Amniotic Adhesion Sequence**
**ADAM: Amniotic Deformity Adhesions Mutilations Complex**
**LBWC: Limb Body Wall Complex**
**OEIS: Omphalocele-Exstrophy-Imperforate Anus-Spinal Defects**

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## Limb Body Wall Complex – Definition:

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DOI: 10.3109/15513815.2015.1055021

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**Possible Genetic Origin of Limb-Body Wall Complex**

David C. Gajzer, Alicia Cristina Hirzel, Gaurav Saigal, Claudia Patricia Rojas, and Maria Matilde Rodriguez

*Department of Pathology, University of Miami, Holtz Children's Hospital, Miami, Florida, USA*

"We believe that including within the LBWC cases with exencephaly, encephalocele and facial clefts without short umbilical cord wrapped around the amnion can be misleading as they seem to be a different defect."

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"We report four cases of LBWC with short umbilical cord wrapped around the extraembryonic coelom, thoracic and/or abdominal wall defects, limb defects, and vertebral malformations, but none of them had facial clefts and each case is characterized by a distinct combination of additional anomalies"

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"This wrong classification could add to the complexity of trying to determine the etiology of these defects."

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***CDX / HOX***
***FGFβ***
***TGFβ***
***BMP4***
***WNT1–8***
***SHH***
***ZIC3***

"We believe that there is a subset of fetuses with the true LBWC that may have undergone a de novo mutation and only a larger series in which molecular studies are performed will lead to enough informative cases to prove our theory of a genetic mutation (…)."

# AIM OF STUDY

- **Review a series of cases with LBWC**
- **Describe the defects identified**
- **Look for predisposing factors (placental abnormalities, maternal context)**
- **Discuss the definition of the complex and its etiopathogenesis**

# MATERIALS AND METHODS

- All autopsies with the diagnosis of LBWC, for the period of **9 years (2008-2016),** were collected from **3 centers**:
  - *Hôpital Femme Mère Enfant, Hospices Civils de Lyon - Centre Hospitalier Universitaire de Lyon* (**HFME - CHUL**)
  - Centro Hospitalar Lisboa Ocidental (**CHLO**)
  - Hospital Prof. Doutor Fernando Fonseca (**HFF**)
- **Autopsies** and **placentas reports, photographs** and **maternal clinical processes were reviewed**
- Statistical analysis (SPSS 22.0; $\chi^2$ test, CI: 95%)

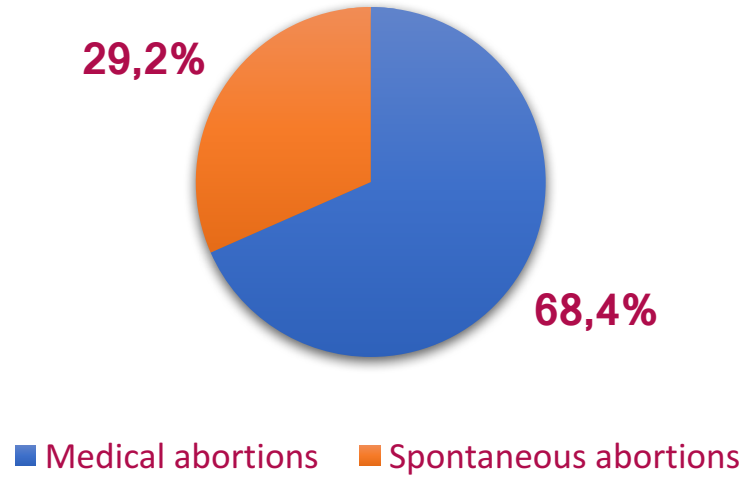
# RESULTS

- **n= 39 autopsies/ 6745 total autopsies (0,6%)**
  - HFME-CHUL: 16/3600 (0,4%)
  - CHLO: 12/ 2197 (0,5%)
  - HFF: 11/ 948 (1,2%)

- **n= 39 autopsies/ 149960 births (2,6/ 10000 births)**
  - HFME-CHUL: 16/ 97200 (1,6/ 10000 births)
  - CHLO: 12/ 17640 (6,8/ 10000 births)
  - HFF: 11/ 35120 (3,1/ 10000 births)

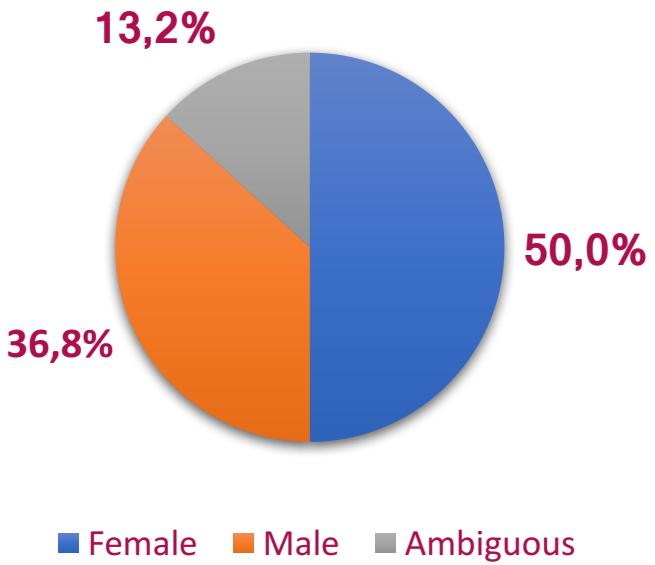
# RESULTS

- **MA (average): 32yo (SD 7,7)**
- **Primigravida: 28%**
  - **55.6% of cases with facial clefts were from primigravida (p=0.021)**
- **Previous abortion: 37%**
  - **None with LBWC diagnosis**
  - **80% of the amputations identified were from mothers with previous abortion (p=0.028)**
- **Maternal diseases: 13,8%**
  - **Maternal diabetes**
  - **Autoimmune disease, NOS**
  - **Unicornuate uterus**
  - **Kidney cyst; recurrent pyelonephritis**



# RESULTS

- **GA (average): 15w (SD 2,9)**
- **Karyotype: without alterations (22 cases)**




| Abdominal/ thoracic wall defect | Limbs defect | Exencephaly/ encephalocele | Facial clefts |
|---|---|---|---|
| 71,8% | 89,7% | 51,3% | 30,8% |
| 48,7% | | | |
| | 28,2% | | |
| 12,8% | | | |
| 10,3% | | | |

# RESULTS

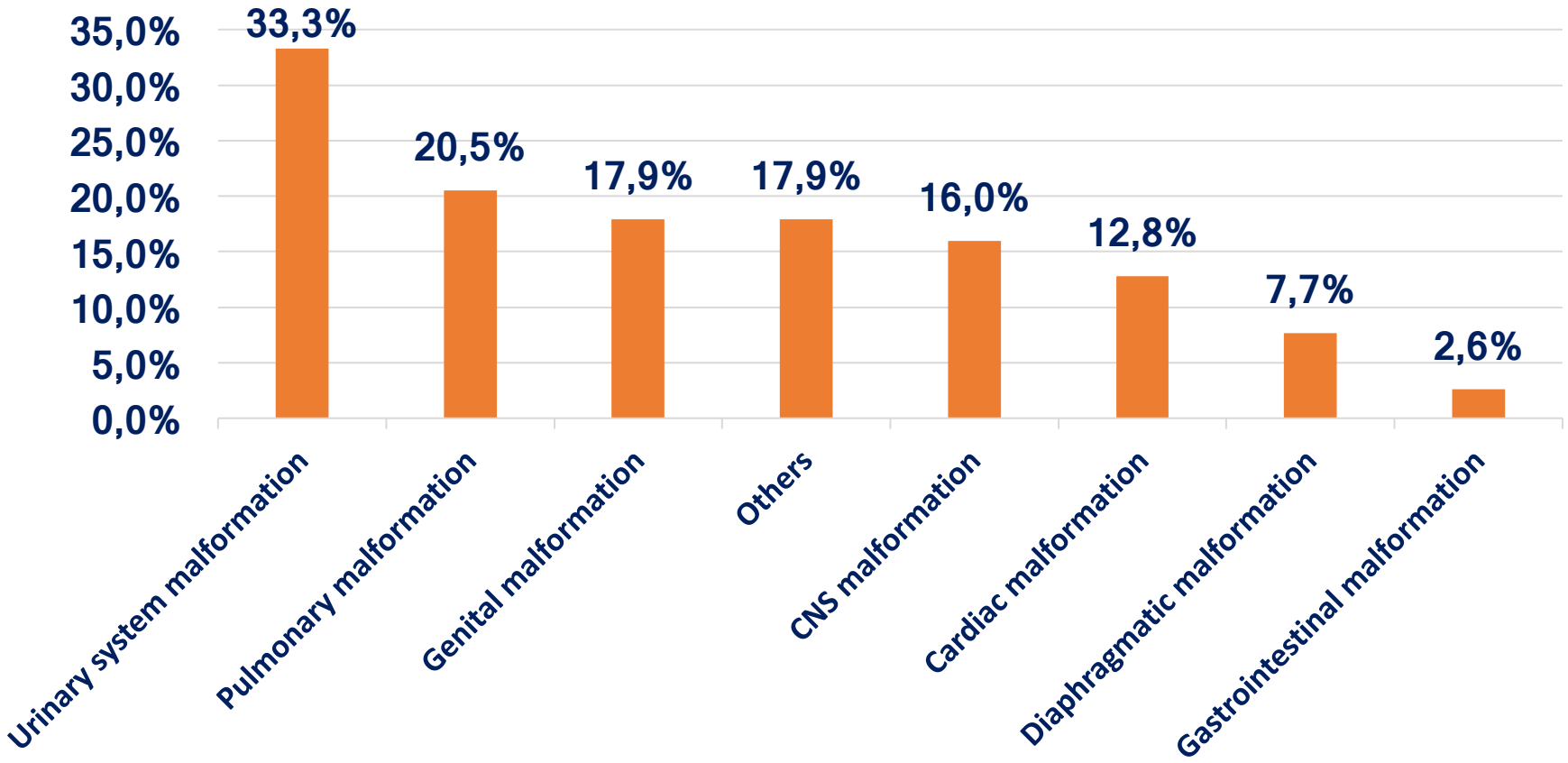
- **70% of cases with exencephaly/ encephalocele didn’t have facial clefts**
- **50% of cases with facial clefts didn’t have cranial defects**

- **Spine curvature changes: 33,3% (scoliosis:lordosis = 5:1)**
- **Amputations: 15,4%**

- **No laterality trend was suggested**

# RESULTS

- **61,5% of cases with visceral malformations**



# RESULTS

- **Placental anomalies: 68,4%**
  - **Short umbilical cord: 63%**
  - **Amniotic band: 42,1%**
  - **Umbilical cord with amniotic membranes: 40%**
  - **Single umbilical artery: 37%**

# RESULTS

| | Abdominal/ thoracic wall + Limbs defects | Exencephaly/ encephalocele | Scoliosis/ Lordosis | Internal malf. | Urinary system malf. | Genital tract malf. |
|---|---|---|---|---|---|---|
| **Short umbilical cord** | 12/16 | 6/14 | 8/8 | 12/14 | 9/10 | 7/7 |
| ***p*** | **0,025** | **0,025** | **0,010** | **0,011** | **0,026** | **0,018** |

- **All cases with amputations were associated with amniotic bands (6/6; p=0.002)**
- **An association between the umbilical cord wrapped around amniotic membranes and amputations seems to exist (3/3; p=0.025)**

# DISCUSSION

## Limb Body Wall Complex:

- **Heterogeneous condition**
- **Equally frequent comparing with the literature**
- **Associations between the foetal findings and the previous abortion / primigravida context – structural cause?**
- **No suggestion of maternal disease / related drugs history**
- **No recurrence recorded**

# DISCUSSION

## Limb Body Wall Complex:

- **Lip / palate cleft: it is necessary to clarify whether it should be included as a major diagnostic criterion or not**
- **High incidence of internal malformations - favours early anomalies of the embryonic disc in origin – Hunter *et al* hypothesis?**
- **High number of cases with urinary malformations**
- **High incidence of placental changes:**
  - **Short cord – diagnostic criterion?**
  - **Single umbilical artery**

# CONCLUSION

- **We favour the theory of primary ectodermal failure in the early embryonic disc suggested by Hunter *et al* (2011)**
- **Multifactorial etiology – molecular and epigenetic features**
- **Complete study of placenta is crucial**
- **Importance of a short cord as a major diagnostic criterion?**
- **Less important role of facial clefts for the diagnosis**

# CONCLUSION

- **Future perspectives:**
  - **Further prospective studies: etiopathogenesis and definition of LBWC (experimental studies in animal models)**
  - **Genetic and molecular studies are needed to clarify the entity and its pathogenesis**

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