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REVIEW

Limb-Body Wall Complex: an Update

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Limb-body wall complex is a complicated fetal malformation with the essential features of : 1) exencephaly/encephalocele with facial clefts, 2) thoraco- and/or abdominoschisis, and 3) limb defect. The diagnosis is based on two out of three of the above features. Prevalent rate varies between 1:4000 to 1:39000 births. Etiology is generally unknown. Chromosome does not play role. Specific teratogen is not proved but cocaine is thought to be possible. Up to date, pathogenesis may be explained by two mechanisms; 1) an early vascular disruption and 2) an intrinsic embryonal maldevelopment. Diagnosis can be made prenatally by ultrasonography. Three dimentional ultrasonography may aid diagnosis. Prognosis is uniformly poor. Termination of pregnancy is the proper management.

Key words: Limb-Body Wall complex, prenatal diagnosis, pathogenesis

Congenital malformations are generally recognizable about 3-5 percent of all births.[1] Causes of congenital malformations are genetic, infection, maternal diseases, drugs, teratogens, multifactorial, and unknown.[1] Limb-body wall complex is the anomaly of unknown etiology.[1-3] It may look unimportant to physicians to understand this anomaly because the prognosis is poor, the management is nothing other than termination, the etiology is unknown, and the prevention is not accessible. However, knowledge is beneficial for further study that more understandable knowledge may overcome the anomaly in future.

Prevalence

Limb-body wall complex is one of the rare congenital anomaly with the varying prevalence of 1:39000 to 1:4000 births.[3-5]

Etiology

The etiology of limb-body wall complex is unknown.[1-3] However, there are two possible etiologic hypotheses include:

1. Vascular disruption in early stage of development[2,3,6]

This theory is proposed by many authors. It is explainable for limb-body wall complex associated with craniofacial defects and amniotic bands and/or adhesion.[6] Van Allen MI, et al found this internal defects that have been recognized as being secondary to vascular disruption up to 72 % of cases in their series.[3] There were experiments in animal models supporting this vascular disruption theory during 4-6 weeks' gestation for the etiologic hypothesis of limb-body wall complex.[7] Maternal cocaine abuse has been proposed to be one of the possible cause in this theory.[3,8] It is explained by its

vasospastic properties that can act as a teratogen by impairing uteroplacental fetal blood flow. Recently, Viscarello RR, et al proposed further evidence of cocaine's teratogenicity by describing two fetuses of limb-body wall complex whose mothers smoked large amounts of cocaine during the first trimester of pregnancy.[8]

Another, but major, point of interest is the coincident amniotic bands and/or amniotic adhesions. This point is a never-ending debate on how come this association does. There are concepts that amniotic bands and/or amniotic adhesions are the results of early rupture of the amnion.[9,10] As well, early rupture of the amnion is proposed to be the cause of early vascular disruption that is the cause of limb-body wall complex.[9,10] Etiology of early rupture of the amnion is unknown.[9,10] However, some authors do not believe this hypothesis and think this may be the consequence from the complex.[11,12] Lately, Moerman P, et al have described it was a pathogenetic overlap. They have proposed that the recognition of constrictive amniotic bands, amniotic adhesions, and limb-body wall complex as discrete but often combined disruption sequences with this important pathogenetic overlap might resolve many dilemmas in interpretation when a fetus exhibited classical constrictive bands beside more severe defects.[13]

***2. Intrinsic embryonal maldevelopment*[2,3,6]**

This theory is explainable for limb-body wall complex without craniofacial defects but presents urogenital anomalies, anal atresia, and abdominal placental attachment.[6] It is suggested that a disturbance of fetal morphogenesis occur before fifth week of development. The pathogenic mechanism of this theory should involve a function in ectodermal placodes.[2] What can be causes in this theory? It remains unknown. Maternal age, paternal age, and familial pattern are not found to be associated.[2,5] Chromosomal defect is believed not to be a causal factor.[2,3,6,14]

Diagnostic criteria

The diagnosis is based on two out of three of the following features:[2,3,6,8]

1. exencephaly/encephalocele with facial clefts,
2. thoraco- and/or abdominoschisis, and
3. limb defect.

The diagnosis, if do not miss, can be made prenatally. Prenatal diagnosis is essential because it leads to early termination.

Prenatal diagnosis

1. Maternal serum alpha-fetoprotein level (MSAFP)

MSAFP level is elevated in limb-body wall complex.[2-4,6,8,9] In hospitals where MSAFP is the screening test in pregnancy, elevated level should also be screened for this anomaly. Negishi H, et al reported that most cases of limb-body wall complex in their series had highly elevated MSAFP level (more than 2.5 multiples of the mean).[14] Gorczyca DP, et al reported that most cases of limb-body wall complex in their series had very highly elevated MSAFP level (more than 10 multiples of the median).[4] It is suggested that an extremely elevated level of MSAFP is also indicative of the complex.[4,9]

2. Ultrasonography

There are many findings that can be evident in the complex, consist of:[14-17]

2.1. Central nervous system abnormalities, detectable features are;
- Neural tube defects : anencephaly, spina bifida, encephalocele.
- Holoprecencephaly (Fig. 1).
- Brain hypoplasia.
- Eye anomalies : anophthalmos, exophthalmos (Fig. 2).

2.2. Craniofacial abnormalities, detectable features are;
- Facial cleft : cleft lip, cleft palate, long deep midline facial cleft (Fig. 2).
- Absence of nose.

2.3. Thoracic abnormalities, detectable features are;
- Thoracoschisis.

- Absence or defects of ribs.
- Ectopia cordis.

2.4. Abdominal wall abnormalities, detectable features are;
- Abdominoschisis (Fig. 3).
- Protruded intraabdominal organs : liver, stomach, intestine (Fig. 3).

2.5. Positional abnormality
- Severe scoliosis.

2.6. Limbs abnormalities, detectable features are;
- Phocomelia.
- Abnormal location of the limbs.
- Constriction of the limbs.

2.7. Amniotic fluid and fetal membrane
- Polyhydramnios may be found due to the coincident neural tube defects and abdominal wall defect.
- Oligohydramnios may also be found due to the coincident amniotic membrane rupture and amniotic adhesion may be detected.

2.8. Umbilical cord
- Short umbilical cord (found 87.5%).[14]

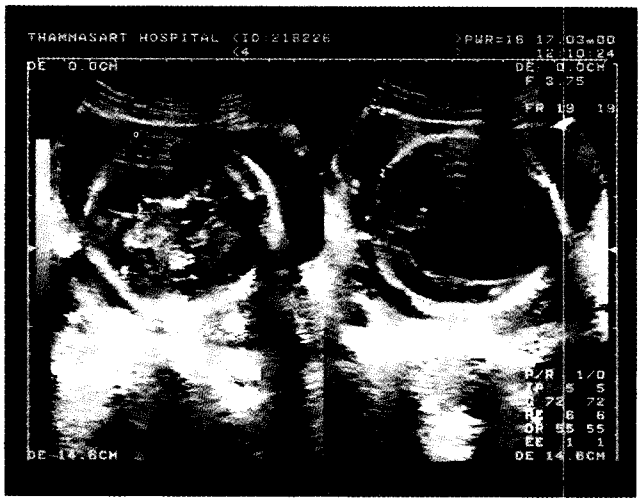

Fig. 1. Ultrasound print showing holoprocencephaly.

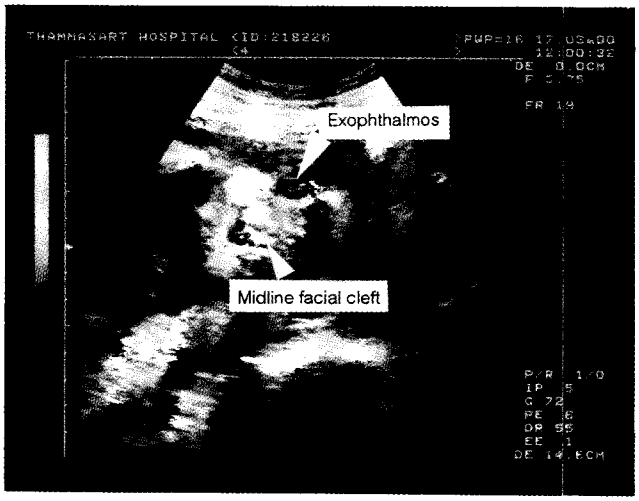

Fig. 2. Ultrasound print showing absence of left eye, enlarged right eye, and facial cleft.

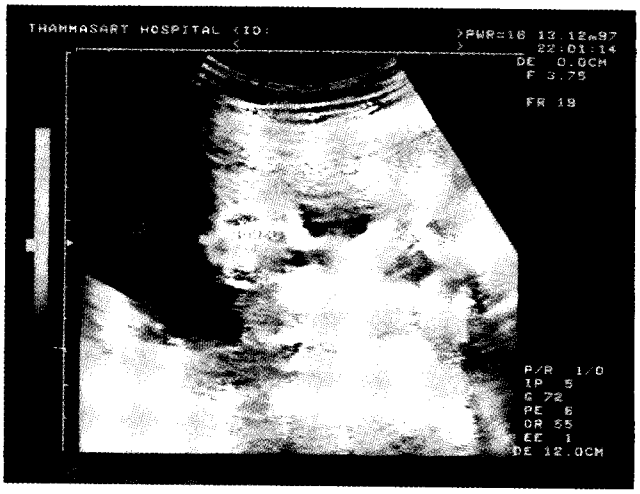

Fig. 3. Ultrasound print showing protruded bowel from the fetal abdomen.

- Single umbilical artery (found 87.5%).[14]

3. Three dimensional ultrasonography

Three dimensional ultrasonography is the more update technology using in obstetrical practice. It is more advantageous in determining surface anatomy. In limb-body wall complex, three dimensional ultra-

sonography adds details about abnormalities in surface anatomy, that are; facial cleft, eye anomalies, chest wall defect, abdominal wall defect, and limb anomalies.[18,19] Three dimensional ultrasonography is clearly beneficial in pranatally diagnose the complex, but the necessitation is in debate because of the cost-benefit reason and the readiness of instrument.[18,19] Up to date, real time two dimensional ultrasonography usually is not problematic in the diagnosis of the complex.[14,15]

4. Fetography

In general, the diagnosis of limb-body wall complex by ultrasonography does not usually present a problem. However, the difficulty inevitably occurs if there is severe oligohydramnios or if there is a very complex relationship between the herniated viscera and the deformities. Fukumasu H, et al proposed that fetography performed in cases of these conditions could obtain a successful prenatal diagnosis of limb-body wall complex.[20]

Postnatal diagnosis

After termination, postnatal diagnosis of limb-body wall complex does not usually have a problem. The diagnosis can be usually made by gross examination. However, autopsy should be performed to confirm the diagnosis.[9,10] There are examples of postnatal gross features of limb-body wall complex showing here. (Fig. 4 and Fig. 5)

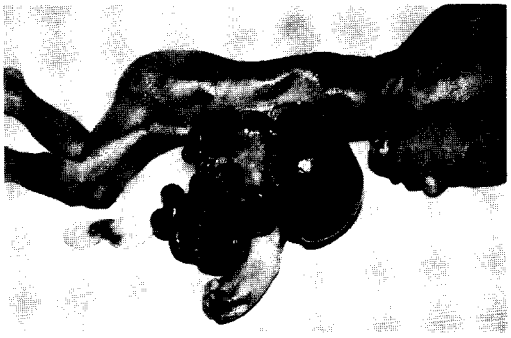

Fig. 4. Picture of the limb-body wall complex baby showing small, distorted, and displaced right upper extremity, scoliosis of thoracolumbar spine, chest wall defect with ectopia cordis, and abdominal wall defect with protruded liver and intestines.

Fig. 5. Picture of the limb-body wall complex baby showing midline facial cleft, absence of nose, left anophthalmos, right exophthalmos, abdominal wall defect, and absence of left upper extremity.

Differential diagnosis

1. Amniotic band syndrome

Amniotic band syndrome is one of the condition with the affected fetus could have very similar clinical features. Its prevalent rate is around 1:5000 births.[21] The fetus with amniotic band syndrome may have limb reduction defects with distortion, constriction, or amputation. The abdominal wall may have defect with protruded intraabdominal organs. There may also be presented with craniofacial anomalies including facial clefts and ocular anomalies. Neural tube defects and cephalocele may coincide. Scoliosis is also evident.[11,21-23] Its hypothesis is thought to be the result of fetal membrane rupture, follows by the decrease of amniotic fluid, fibrous band and adhesion formation, and finally, the amputation effect.[11,21] Up to date, it is still believed that limb-body wall complex is different from amniotic band syndrome.[11] The diagnosis, either prenatal or postnatal, must be thoroughly distinguished. There is no specific clue, however, it should be mentioned here, as follows;[11,21-24]

- Amount of amniotic fluid should be found decreasingly in amniotic band syndrome. In limb-body wall complex, amniotic fluid may be either decreased or increased.

- Amniotic band and adhesion are more commonly detectable in amniotic band syndrome than in limb-body wall complex.
- Limb defects usually are more prominent in amniotic band syndrome, especially are affected in many limbs.
- If holoprocencephaly is detected, the likelihood of limb-body wall complex is stronger.

2. Pentalogy of Cantrell

Pentalogy of Cantrell is the combinations of abdominal wall defect with omphalocele, ectopia cordis, diaphragmatic hernia, intrinsic heart anomaly, and pericardial effusion. The parts possibly detected in both limb-body wall complex and pentalogy of Cantrell are abdominal wall defect and chest wall defect. The ways that can assist in differential diagnosis are;[25-27]

- Ectopia cordis is less commonly found in limb-body wall complex.
- Degree of suspicion is decreased for pentalogy of Cantrell if the protruding visceral organs are not covered by omphalocele, but is more possible in limb-body wall complex.
- Diaphragmatic hernia, intrinsic heart anomaly, and pericardial effusion should be screened.
- Limb anomalies and scoliosis, if detected, are likely to the diagnosis of limb-body wall complex.

3. Trisomy 13

Holoprecencephaly can be evident in both limb-body wall complex and trisomy 13. It is reported that holoprocencephaly has been found in trisomy 13 for 24 percent.[28] Once holoprocencephaly is detected, chromosome study might be indicated. However, if ultrasound screening is detailed, diagnosis of limb-body wall complex can be made without necessitation to perform chromosome study. In contrast, associated numerous major and minor malformations are the most prominent factors leading to the diagnosis of chromosome abnormalities, examples; cleft lips, intrinsic heart abnormalities, and increased nuchal fold translucency.[28,29]

4. Omphalocele and Gastroschisis

If abdominal wall defect is sonographically detected, obstetrical ultrasonologists should search for associated malformations. If abdominal wall defect is a part of limb-body wall complex, the case is properly managed by termination. If not, conservative management must be discussed and chromosome study may be indicated.[17,25,26]

Prognosis

Prognosis is uniformly poor. All cases of limb-body wall complex are not able to survive.[2,3,6,16]

Management

Up to date, the management of the complex is still limited by termination.[2,3,6] Fetal therapy and post-natal correction are not possible. Early termination is the only beneficial management that physicians should offer to the mothers because early termination will reduce maternal complications and psychological trauma. Counseling on pathogenesis is often helpful to the couples. Complete review of the history on what possibly associable cause (example; cocaine abuse) is beneficial. Firstly, to the parents, stopping those behaviors will aid in the prevention of recurrence in the next pregnancy. Secondly, to the public, more and more update knowledge will be discovered and it may lead to understand more about the complex.

Conclusion

Limb-body wall complex is a complicated fetal malformation with the essential features of : 1) exencephaly/encephalocele with facial clefts, 2) thoraco- and/or abdominoschisis, and 3) limb defect. The diagnosis is based on two out of three of the above features. Prevalent rate varies between 1:4000 to 1:39000 births. Etiology is generally unknown. Chromosome does not play role. Up to date, pathogenesis may be explained by two mechanisms; 1) an early vascular disruption and 2) an intrinsic embryonal maldevelopment. Diagnosis can be made prenatally by ultrasonography. Prognosis is uniformly poor. Termination of pregnancy is the proper management. Knowledge about the complex is beneficial for further study.

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