Complex of amniotic deformities, adhesions, mutilations: endless debate

Zulema Ivón Rodríguez González, Fernando Soriano Padilla

Universidad Autónoma de Ciudad Juárez, Instituto de Ciencias Biomédicas, Ciudad Juárez, Chihuahua, Mexico

Cirugía Maxilofacial Pediátrica, Unidad de Medicina de Alta Especial, Hospital de Pediatria, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, Mexico City, Mexico

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Abstract  Amniotic deformities, adhesions, mutilations (ADAM) complex is a broad heterogeneous spectrum of congenital anomalies. ADAM complex is characterized by constriction rings, amputation of fingers or limbs and the presence of the amniotic band. However, it may also involve craniofacial disruptions, body wall defects and internal organ abnormalities. The aim of this review is to present the results found in regard to ADAM complex from its historical background, clinical manifestations, epidemiology, etc. In particular, our attention was focused on demonstrating the varying etiopathogenesis theories of ADAM complex and their contradictions. The study was conducted using the databases of PubMed, EBSCO host, Ovid, SpringerLink, Scopus, nature.com, JAMA and ScienceDirect with the following keywords for the search: “amniotic band syndrome”, “amniotic band sequence”, “Streeter dysplasia”, “ADAM complex”. In this study we used 22 full-text articles.

Patients with ADAM complex require a complete pre- and postnatal evaluation to integrate the diagnosis and to decide on timely treatment. It is important for clinicians and surgeons to possess knowledge of this entity. Further research is necessary to establish a nosological basis.

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* Corresponding author.
E-mail: drazulemarodriguezg@gmail.com (Z.I. Rodríguez González).

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1. Introduction

Amniotic deformities, adhesions, mutilations (ADAM) complex is a set of abnormalities that can be manifested from constriction bands in the fingers or limbs up to their amputations. It is also associated with other manifestations of the face, chest and abdomen. Diagnostic criteria are purely clinical and pathogenesis is based on two main theories: intrinsic and extrinsic. From these theories, other complementary theories arise. Despite the variety, none justifies the abnormalities as a whole; therefore, prenatal diagnosis still remains difficult. The prognosis depends on the severity of anomalies present, affecting aesthetics, function or demonstrating incompatibility with life. The objective of this review was to present data found in the different databases on ADAM complex: historical background, clinical manifestations, epidemiological studies, diagnostic criteria, and prenatal diagnosis. Special attention was given to show the different theories and hypotheses of the pathogenesis as well as their contradictions, arguments and vague concepts involving this entity.

2. Methods

The search was conducted in PubMed databases, EBSCO Host, Ovid, SpringerLink, Scopus, nature.com, JAMA and ScienceDirect using the following search keywords: “amniotic band syndrome”, “amniotic band sequence”, “Streeter syndrome”, “ADAM complex”. For this study, those articles with complete text from 2009 through 2014 were used. A total of 22 articles were taken into consideration.

3. Results

It is known that this complex has a broad and heterogeneous spectrum that involves three types of anomalies: deformations, malformations and disruptions. It occurs sporadically although cases have been reported with a hereditary tendency. In 1992, Moerman et al. proposed the ADAM complex as a collection of three manifestations: constricting bands of tissue, amniotic adhesions and in a higher complex, the limb-body wall complex. The syndrome is known by multiple synonyms: amniotic band syndrome (by Chemke et al., 1973; Kino, 1975; Ossipoff and Hal, 1977; Seeds et al., 1982; Fiedler and Phelan, 1983), amnion rupture sequences, amniotic band sequence (by Hunter and Carpenter, 1986; Kalousek et al., 1988), ADAM complex (by Herrmann and Opitz, 1983), amniotic deformities, adhesions, mutilation. It is also known as amniotic disruption complex (Higginbottom et al., 1979), amniotic band lesions, annular grooves, congenital amputation, congenital constriction bands, transversal defects of the extremities, body wall defects with deformities of the extremities (Pagon et al., 1979), body wall complex of the extremities (Van Allen et al., 1987), aberrant tissue bands, Streeter syndrome, Streeter bands or bridles, amniotic band spectrum, Streeter dysplasia, genetic constriction band syndrome and amniochonoric mesoblastic fibrous chains. It is classified as number 217100 from the OMIM and Q79.80 from the International Classification of Diseases (ICD-10). The different theories of its pathogenesis explain why there are >30 synonyms for this named disease.
3.1. Historical background

There are many contributions and investigations about ADAM complex throughout history. Therefore, only a few will be mentioned. The first reports of this pattern of malformations were probably those of Portal,\textsuperscript{19} The practice of deliveries supported by a large number of observations, in 1685. The first theory of pathogenesis was proposed by Montgomery\textsuperscript{19} in 1832, which attributed the annular constrictions and other fetal alterations to an inflammatory process as its origin.\textsuperscript{20} The first theory proposed of “failure in development” was made by Sir James Simpson\textsuperscript{20} in 1836. Later, in 1930, the works by Streeter were published with his intrinsic theory.\textsuperscript{21} In 1965, Torpin associated defects of the extremities or their amputations with amnion rupture and bridle compression to the extremities.\textsuperscript{22} Hermann and Opitz used the acronym of the ADAM complex to describe it.\textsuperscript{23} Kino carried out experimental studies in animal models and began to mention vascular disruption.\textsuperscript{4} Keller et al. discussed the association of cleft palate and lip and other facial disruptions with constriction bands generally supporting the non-hereditary nature.\textsuperscript{24} Poland et al. linked the vascular compression mechanism with these anomalies.\textsuperscript{25} The theories proposed by Van Allen et al. about vascular disruption\textsuperscript{26} should not be omitted or the contributions by Bamforth on the alterations in the morphogenesis of the primary stage of gastrulation.\textsuperscript{26}

3.2. Epidemiology

Froster and Baird,\textsuperscript{27} in a study carried out from 1952-1984 in British Columbia, found a minimum incidence of 1:50,579 with a hereditary tendency, whereas Garza et al.\textsuperscript{28} published an epidemiological study in which they used as a minimum criteria the amputation or constriction bands in a sample of 388,325 live newborns (LB) between 1968 and 1982 in Atlanta. The prevalence was 1.17/10,000 LB. Subsequently, Orioli et al.,\textsuperscript{29} in the Latin American Collaborative Study of Congenital Malformations (ECLAMC) in Rio de Janeiro, Brazil, from a database of 3,020,896 LB and newborns who died from 1982-1988, found a prevalence of 1:11,200. Finally, mention should be made of the work by Guzmán-Huerta et al.\textsuperscript{30} from the Medicina Materno Fetal, Instituto Nacional de Perinatología Isidro Espinosa de los Reyes, México, D.F. (Department of Maternal Fetal Medicine, National Institute of Perinatology “Isidro Espinosa de los Reyes”, Mexico, D.F.) who, using a database of 90,000 LB during a 17-year period (January 1993-July 2010) reported a sample of 50 cases diagnosed with amniotic band sequence, obtaining an incidence of 1:2,000 LB.

Although several authors have reported that there is no gender prevalence, in studies by Garza et al.\textsuperscript{31} a prevalence of 1.44 for females and 0.91 for males was observed. Moreover, Guzman-Huerta et al. found that 44% were female, 38% male and gender was not able to be determined for the remainder.\textsuperscript{32}

3.3. Diagnostic criteria and clinical manifestations

Diagnostic criteria are unclear and are not well established. Martinez Frias believes, based on epidemiological studies, that those manifestations of ADAM complex with the presence of wall defects should be considered to be different entities.\textsuperscript{33} This has been the subject of many discussions as there are authors who still consider it to be the same entity but with variable expression.\textsuperscript{31-35}

Van Allen et al. concluded that, for the diagnosis of ADAM complex, at least two of three manifestations are needed: exencephaly/encephalcele with facial clefts, throracocis/s abdominoschisis and defects of any kind in the extremities.\textsuperscript{13,25,35} The clinical features of this sequence are not identical in any of the cases reported, as the variability and severity of ADAM complex will be defined according to the time of gestation in which the damage occurred; hence, phenotype diversity. According to Orioli et al., the extremities are affected in 71.9% and occupy first place as manifestations of amniotic bridles in their study. Defects of the extremities can present as reduction (mutation) of extremities, bridles or their amputation, constriction bands in the extremities (deformities),\textsuperscript{29} lymphedema distal to the constriction band, distal syndactyly, acrosyndactyly or clubfoot. There have been less common anomalies such as oligodactyly, preaxial polydactyly,\textsuperscript{36} arthrogryposis, single bone in the forearm, hypoplasia of the radius and/or ulna and ectodactyly.\textsuperscript{37}

Craniofacial anomalies occur in a smaller percentage according to the study by Orioli et al.\textsuperscript{29} In contrast to this, Guzman-Huerta et al. obtained a rate of 78%.\textsuperscript{30} Craniofacial disruptions are also highly variable. There have been cases of microcephaly, encephalcele, defects in the anterior portion of the shell, typical and atypical craniofacial fissures with aberrant bands of tissue around the face,\textsuperscript{27} cleft lip and palate, colobomas of the eyelids and ectropion. Ophthalmological conditions have been described ranging from dysfunction or absence of the nasolacrimal duct to ptosis, although there have been cases of anomalies reported where the ocular globe is involved such as defects of the iris and of the optic nerve.\textsuperscript{30} Ocular deformities of corneal opacity can be acquired or secondary to exposure. Deformations of eye corneal opacity may be acquired or secondary to exposure. Bilateral epibulbar choristomas have also been described as well as corneal leukemia, all associated with ADAM complex.\textsuperscript{36-38}

Various malformations have been associated. For example, holoprosencephaly,\textsuperscript{4} Dandy-Walker malformation, septo-optic dysplasia, clover-leaf-shaped skull (Kleeblattschädel), hydrocephalus, hypertelorism, uveal coloboma, choanal atresia, unilateral proboscis, low set ears, Robin sequence, Potter deformities and other deformities.\textsuperscript{31} Various wall defects have been described: thoracocis, abdominoschisis, thoracoabdominoschisis, ectopia cordis, gastrochisis, omphalocle, multiple cardiovascular malformations, tetralogy of Fallot,\textsuperscript{31} abnormal pulmonary lobulation, abnormal or absent diaphragm, abnormal intestinal rotation, anal atresia, absence of gonads, abnormal external genitalia and scoliosis.\textsuperscript{37}

3.4. Etiology

The pathogenesis of ADAM complex has been widely discussed and has been divided into two main groups or classical theories: the intrinsic model by Streeter\textsuperscript{21} and the extrinsic model by Torpin.\textsuperscript{22} However, there are other contributions that for decades have been relevant.\textsuperscript{13}
The intrinsic model proposed in 1930 and also known as endogenous theory, theory of germinal disk dysplasia or embryonic dysplasia explains that the anomalies and fibrous bands have a common origin and are caused by histogenesis imperfection and damage in the germinal disc during early embryogenesis. The author also adds that it has been confused with amniotic bands that, in reality, represent residual tissue of the localized area of defect. The theory was based on macroscopic and microscopic observation of 16 constrictions. On the other hand, in the observational study by Torpin, the author supported that the anomalies of ADAM complex are caused by fibrous bands of amniotic tissue as a result of amnion rupture followed by the loss of amniotic fluid, i.e., of an oligohydramnios and, at the same time, extrusion or expulsion of the entire fetus or parts of the fetus towards the chorionic cavity. Fetal extremities are trapped by these fibrous bands causing compression and necrosis or amputation of fingers or extremities and referred to by some authors as mechanical disruption, theory of amniotic disruption or exogenous theory.

Van Allen et al. in 1987 contributed the theory of vascular disruption, with a background by Kino in 1975 with animal model experiments. Van Allen et al. report that vascular damage or alterations in the morphology of blood flow during embryogenesis leads to disruption in morphology or necrosis or destruction of existing structures. Later, in another article, these authors mentioned that vascular disruption may also give rise to cleft lip and palate. Hunter et al. proposed another theory, which is said to have similarities to the theory proposed by Streeter. They explained that it is an early primary defect/deficiency of the ectoderm of the embryonic disc in embryogenesis. The area affected along with the severity of the results vary according to the location of the defect. The authors focused primarily on craniofacial anomalies and separated them as follows:

1. Exencephaly/encephalocele with amniotic connections without facial clefts
2. Similar cranial lesions with facial clefts with or without amniotic bands
3. Abdominoschisis and thoracoabdominoschisis
4. Anomalies of the extremities

For the first group, a deficiency in the response and growth of the ectodermal cells would give rise to neural tube defects commonly seen with ADAM complex. That is, a minimal deficiency in the growth of the ectodermal cells, whether from one side to the other and/or anterior to the oropharyngeal membrane, could result in an amnion-ectodermal margin that would be close or in direct contact with these cells and would explain the cranial defects such as exencephaly/encephalocele and the bands adhered to this region. For the second group, cranial lesions with facial clefts with or without amniotic bands explain the following. Facial clefts generally involve fusion plates of the frontonasal processes and association with organs with the anterior brain. The frontonasal processes derive from neural crest cells, which surge from the fusion of the neuroectoderm in the region of the forebrain. The same deficiency of the ectoderm could lead to a neural crest deficiency and affect the frontonasal processes. In a similar manner, the ectodermal deficiency could result in a connection of the neural-amnion tubes. A deficiency of the anterior ectoderm of the oropharyngeal membrane could bring the amnions abnormally close or in direct contact with the oropharyngeal membrane: the amnion would interfere in the margins of the frontonasal/maxillary planes in their development and closure. This could explain why some clefts extend up to the base of the skull and the aberrant amniotic tissue bands over the facial clefts.

Finally, Romero-Valdovinos et al. presented a hypothesis centered on the epithelial-mesenchymal transition processes (EMT), which act during organogenesis in the adequate formation of the different organs in the three embryological stages. If these EMT are altered, they propel the immobile epithelial cells into acquiring a polarity and migratory characteristics similar to fibroblasts. The proposal mentions that the ADAM complex could be considered as a variation of fibrosis due to a complication of fetal membrane rupture in a pathological state of pregnancy. The reason for the membrane rupture is unknown, but an intrauterine infection during pregnancy could cause weakness of the fibrous components of the choioamniotic membrane and consequently loss of integrity, initiating the activation, proliferation and migration towards the wound and the synthesis of elevated levels of extracellular matrix proteins (profibrotic and antifibrotic) including collagen and fibronectin. TGF-β (transforming growth factor β) family is the main route for the EMT regulation. Excessive deposition of extracellular matrix isolates the parenchyma from the oxygen supply. Therefore, it leads to tissue hypoxia, damage of the parenchyma and also fibrinogen stimulation. EMT are critical for embryonic and fetal processes as well as for wound healing and tissue repair. EMT are involved in gastrulation, neural crest migration, neural tube formation, formation of the heart, and closure of the palate and may also explain the formation of fibrosis, presence of bridges and alteration in cell migration that cause anomalies in internal organs.

### 3.5. Classifications

There are various classifications, e.g., those classified according to the time of disruption and the result of the anomalies. Prenatal classifications of Weinzieg, Hüsler et al. and others focused on the affected extremities are the best known. The prenatal classification of Hüsler and Weinzieg et al. is divided into stages and done by ultrasound:

Stage 1. Amniotic band without signs of constriction
Stage 2. Constriction without vascular compromise (normal vascular Doppler studies), although there may be distal deformity
Stage 3. Severe constriction with progressive arterial compromise: arterial flow must be measured in the proximal and distal portion of the constriction; this stage is subdivided into two types:
- Type 1: Distal anomalies when compared with the Doppler study of the contralateral extremity
- Type 2: Extremity without vascular flow
Stage 4. Tendency towards fracture in the long bones at the site of constriction
Stage 5. Intrauterine amputation
The classification by Isacsohn et al. is based on the depth of the band. These authors divided it into five groups:

1. The band is only a groove in the skin.
2. The band involves the subcutaneous and muscle tissue.
3. The band extends to the bones.
4. There is a pseudarthrosis.
5. Uterine amputation occurred.

The objective of the Paterson classification was to describe the severity of the distal deformities of the extremities. It is summarized into four groups.

Group 1: Extremities with simple rings of constriction with the distal portion intact, with a degree of depth of the ring only to the subcutaneous level
Group 2: Constriction ring with distal deformity including atrophy, and lymphedema
Group 3: Constriction ring associated with acrosyndactyly
Type I: Fingers joined with tissue of adequate depth
Type II: Fingertips are well joined but the tissue is not good or is not complete
Type III: Fingertips are joined but with sinus tract between them (acrosyndactyly and distally syndactyly with the distal portion of the fingers being fused and the proximal portion separated)
Group 4: Amputation at any level of the limb or digit

There is another proposed classification based on the morphological findings found in the study by Guzmán-Huerta et al. These authors separated the cases according to phenotype findings:

Phenotype I. Craniofacial defect + defect of the extremities
Phenotype II. Craniofacial defect + defect in the extremities + defect in the abdominal wall, spine and/or thoracic defect
Phenotype III. Defect in the extremities + abdominal wall defect, spine and/or thorax
Phenotype IV. Isolated defect (craniofacial, in extremities or body wall). This classification has as objective the diagnosis and probability of recurrence.

3.6. Maternal risk factors

Proposed risk factors are multiple. Risks have been cited from oophorectomy, abdominal trauma, uterine malformations, use of intrauterine drug, disease ingestion such as clomiphene and contraceptives. Others have been found such as invasive procedures: septotomy, twin to twin transfusion syndrome and amniocentesis in case of chorionic villus biopsy. However, other factors have been attributed such as results of epidemiological studies. Such is the case of the work by Orioli et al. where primigravida mothers presented a risk two times greater than multigravida mothers, with statistical significance (OR: 2.16; CI 95%: 1.25-3.72). Another of the factors was having fever during the first 3 months of gestation (OR: 9.0; CI 95%: 1.25-394.48), which increased the risk nine times. Intake of medications (OR: 2.38; CI 95%: 1.32-4.26) as well as vaginal bleeding during the first trimester of gestation (OR: 2.00; CI 95%: 1.00-4.00) and a nonces-
complex. This method helps to detect severe defects or defects incompatible with life, which occur in the early period of gestation.\textsuperscript{50}

3.8. Differential diagnoses

ADAM complex defects could mimic conditions from frontonasal dysplasia, Meckel syndrome arthrogryposis and Ehlers-Danlos type IV syndrome.\textsuperscript{77} Other differential diagnoses should be made with the “Michelin baby” syndrome or benign multiple circumsferential skin grooves syndrome, Adams-Oliver syndrome, oromandibular limb hypogenesis syndrome, with the disorganization syndrome as homologous of the genetic entity described in mice\textsuperscript{46} and, finally, of the body wall-extremity complex from which various authors have differentiated it\textsuperscript{11,12,14} and which for others are synonymous.

3.9. Prenatal treatment

Fetoscopy, according to some authors, should already be offered as part of the prenatal treatment. Others believe that there are currently no supported studies with respect to elimination of the constriction bands with fetoscopy. Publications have been limited to reports of clinical cases\textsuperscript{51}; in addition, many hospitals do not have the infrastructure for the possibility of performing fetoscopy. Guzmán-Huerta et al.\textsuperscript{20} presented a flowogram where the prenatal protocol to follow was described from the time in which the amniotic band is localized on ultrasound. Subsequently, taking into account the location and number and thickness of the band as well as the morphological conditions found in the fetus, i.e., if the fetus presents defects of the extremities, craniofacial region and body wall/spine, it is classified according to its phenotype, if it is compatible with life or if there is some constriction of the extremity or of the umbilical cord. Only for Stages 2 and 3 of the Weinzweig classification or those in which there is the short umbilical cord is the indication for a fetoscopy evaluated. The flowgram allows making decisions from the imaging results. It is also essential to have a team of specialists in maternal-fetal medicine, fetal surgery and pediatric surgery, neonatology, radiology and genetics.\textsuperscript{10}

4. Discussion

Having reviewed the data, population and methodology of epidemiological studies and taking into account the associated risk factors, the incidence found in different studies is so varied that the results obtained by each author is not surprising.

A big difference is noted with regard to the most common manifestations of the amniotic bridge syndrome. In the study by Orioli et al.,\textsuperscript{29} the extremities were the most affected, whereas in the results by Guzmán-Huerta et al., the craniofacial defects represented 78\%, followed by defects in the extremities with 70\%.\textsuperscript{39} What is of note is that craniofacial manifestations were in the minority according to the results of Orioli et al.,\textsuperscript{29} which leads to review of the specifications of each author. For Guzmán-Huerta et al.,\textsuperscript{33} the group of craniofacial defects included facial disruption, acrania, cleft lip and palate, facial disruption, defects in the ears, eye and/or nose, choanal atresia, craniosynostosis, ventriculomegaly and/or hydrocephaly and holoprosencephaly. In turn, Orioli et al.\textsuperscript{29} separated in groups the neural/cranial defects, facial clefts, facial asymmetries and manifestations in specified areas such as the eye and the ear. When added, there were 94/284 cases; however, in comparison, this number continues to be lower. This raises the question of whether this difference is related to environmental, genetic or ethnic factors or to differences between the size of the sample. It was also noted that the results of Guzmán-Huerta et al.\textsuperscript{26} and of Werler et al.\textsuperscript{32} coincided with those of Orioli et al.\textsuperscript{29} in some of the factors that increased the risk, such as nulliparous, maternal race (black) and young mothers.

The etiology has been the most controversial. Higginbottom et al.\textsuperscript{11} supported the Torpin theory with his observational study of 79 patients with ADAM complex. Of these, 54 presented with multiple system involvement and in 25 cases only the extremities were affected. The authors highlight that the facial clefts were unusual and did not follow the closure pattern. This observation was made earlier by Jones et al.\textsuperscript{33} who presented seven patients with a pattern of craniofacial anomalies also associated with involvement of the extremities. They claimed that the anomalies were secondary to the disruptive forces of the aberrant tissue bands. In their discussion they determined that the evidence supporting this theory was that the location and extent of the facial clefts in the cases presented are unusual, and none had the normal planes of closure of the facial processes. Therefore, the following questions arise: what triggers or makes the difference between facial clefts with closure patterns and other bizarre results? What process or mechanism makes them different? In the study by Orioli et al.,\textsuperscript{29} of the 284 cases of ADAM complex, 33 cases were the total of facial clefts. Of these, 18 cases corresponded to cleft lip/palate or without palate, and 15 cases to atypical facial clefts. As can be seen, there are multiple cases reported with typical facial clefts and other bizarre results such as those presented by Higginbottom et al. and Jones et al.\textsuperscript{11,53} Of course, one has to rule out the isolated clefts. It would be logical to think that the same factor or disruption would be repeated in the three or, perhaps, should the possibility be raised of three distinct etiologies for each type of facial cleft?

Another important point that revokes the Torpin theory is that Van Allen et al.\textsuperscript{11} noted that amniotic bands were present in only 40\% of cases and that 95\% had internal defects. These characteristics could not be attributed to amniotic bands. Finally, there are anomalies that cannot be explained with the amniotic disruption, such as the cases presented by Halder with an added tetralogy of Fallot.\textsuperscript{25,31}

With regard to the theory of vascular disruption, it is noteworthy that Daya and Makakole\textsuperscript{36} examined ten patients with a total of 20 limbs affected by amniotic bands. MRI angiography or CT scan should be carried out in order to evaluate arterial blood flow in the limbs. The study found that vascular anomalies could be caused by vascular disruption. Vascular abnormalities were found in all patients and these increased according to the depth of the band. It was concluded by accepting that the depth of the band is an indicator of intrauterine damage and a marker of underlying anomalies. It was noted that it is easy to explain the vascular abnormalities as an effect of ADAM complex, but it can-
not be excluded as an associated cause although the theory of vascular disruption alone cannot explain the other clinical manifestations such as encephalocele, oblique facial clefts, number of abnormal umbilical vessels or clubfoot (which is present in 33% and is closely related to oligohydramnios).

Another weak point of vascular disruption is the lack of clarity as to whether the vascular disruption is primary or secondary to the fibrous bands. Werler et al.\(^5\) compared the epidemiological characteristics between defects in the reduction of extremities + amniotic bands and those with transverse defects of the extremities without amniotic bands to determine whether maternal exposures of these groups support the hypothesis of vascular disruption. If the amniotic bands were secondary to vascular alterations, then a shared pathogenesis for each group would have similar risk factors. The results of this study contradicted the hypothesis that Werler et al. proposed, as demographic patterns, reproductive patterns and vasoactive risk factors in both groups did not converge so that what increased the risk for one group had no effect on the other. Therefore, the authors suggested that ADAM complex with abnormalities of the extremities, without evidence of amniotic bands, could be different entities.\(^5\)

Streeter’s theory was not subject to the 1930 limitations, but there were several studies since then. McKenzie, who supported this theory, added that during embryogenesis a physiologically normal, programmed cell death takes place, for example, in the interdigital spaces for the development of soft tissue of the digits. The defect in these arises through the cellular material that remains in varying degrees in the interdigital spaces so that the result will be syndactyly or bands. The author also explained that the tissue defect at the site of constriction reflects an abnormal distribution of the areas of cell death.\(^5\) Hartwig et al.,\(^5\) supporting the Streeter theory, presented their theory of ectodermal placodes. The authors argued that these are involved in the formation of many organs and structures including the neural tube, nose, brachial arches, ventral wall of the body and extremities; therefore, a malfunction or defects of the ectodermal placodes will result in corresponding anomalies.\(^31,5\)

Bamforth found that the mechanical force compromises the fetal vasculature or a discrete lesion interferes with development of the germinal disc.\(^26\) Many of the defects are explained by intervening in neuropore closure, failure in the migration of neural crest cells and damage of the (please translate mesofrodos), which consists of local interference of the levels of organization of gene expression during early embryogenesis before effective embryonic circulation is established, i.e., prior to the 26th day after fertilization. Halder, among others, tried to explain the clinical manifestations of their cases with the theory proposed by Streeter.\(^31\) On this basis, it is argued that this theory could explain in a joint fashion the anomalies present: amniotic bands, rudimentary limbs and, in particular, internal organ malformations.

The assertions by Hunter et al. show that there is no correlation between craniofacial defects and those of the extremities. They disagree with the idea that a single mechanism can explain the spectrum of associations found. Precisely, this is what has prevented the discovery of the pathogenesis. Thus, they have separated each anomaly for explanation based on the fact that the embryological origins of each are different.\(^35\) However, similar questions continue such as what determines the fact that some cases present greater severity than others? The authors explain that this depends on the location in the deficiency of the ectodermal cells affected. So what would be the cause or origin of the severity?

Romero-Valdovinos et al. explained the participation of the epithelial-mesenchymal transition processes, proteins and other cell mediators, which may contribute to the pathogenesis of ADAM complex.\(^46\) It would be interesting, however, to find other studies that address the theme or future research that may give way to his theory.

In the classification by Isacsohn et al.,\(^44\) it is highlighted that the increase in the depth of the band results in a greater distal severity with lymphatic, vascular and nerve compromise. Daya and Makakole\(^44\) observed this in their study where the depth of the band is directly related with the vascular anomaly of the extremity. They also found that, in the majority of cases, the abnormal vascular anatomy would occur at a distance proximal to the band, presenting absence of main vessels to absence of branches and atresia of segments in greater arteries, among others. This, of course, cannot be ignored for the planning and decision making regarding the surgical procedures. Thus, the Patterson classification has also been of assistance for orienting the procedure to follow, such that grade I and IV have no surgical indications, whereas grades II and III could benefit from early intervention.\(^45,57\)

It is obvious that there are many attempts to classify the ADAM complex. The history of the Guzman-Huerta classification was proposed by Garza et al. in 1988 and by Russo et al. in 1993. The latter secured the evidence of two phenotypes clearly distinguishable from the body wall-extremity complex of phenotype 1 in which craniofacial defects and amniotic bands and/or adhesion are shown and phenotype 2, without craniofacial defects and with the presence of urogenital abnormalities, anal atresia and abdominal detachment of the placenta as well as the persistence of a extraembryonic coelom. They suggested that these two phenotypes are a consequence of two different pathogenic mechanisms.

Currently, the body wall-extremity complex and ADAM complex are not defined as separate entities. Again, the questions arise:

- Where does the difference occur during embryogenesis?
- What mechanism(s) or factor(s) in embryogenesis affect and make a difference?
- What are the clinical manifestations of each entity?

Jamsheer et al.\(^32\) carried out a study with the objective of evaluating if there were considerable differences in the clinical pattern of the congenital abnormalities of the extremities and abnormalities of internal organs among patients with characteristics of ADAM complex + defects of the body wall and those patients with characteristics of ADAM complex but without wall defects. They observed that cases of ADAM complex + body wall defects are commonly affected by internal congenital abnormalities, especially by urogenital malformations and that in both groups the reduction of the extremities occurs in 80% of the cases. However, minor defects and distal extremities (amputation of the fin-
gers, pseudodactyly, constriction rings) predominated in the ADAM complex group without wall defects. They finally concluded that ADAM complex occurred during embryogenesis at a stage later than those with ADAM complex + body wall defects. This study shows that both groups represented two nosologically different entities. Jamshieer et al.\textsuperscript{33} made reference to the works by Martínez-Frias who had already declared the difference of the two entities based on a clinical and epidemiological analysis.\textsuperscript{31}

Advances in imaging and MRI have led to these procedures being part of the useful tools in prenatal diagnosis. Ultrasonography remains a fundamental pillar in fetal diagnosis. Despite its progress, it is still difficult to identify constrictive bands and visualization of anomalies, especially those of the craniofacial region but we also have the use of complementary methods that provide more detail on fetal morphology, especially for the craniofacial and neck regions.\textsuperscript{34} These methods are also useful for surgical planning in cases where fetal surgery is contemplated, although once involvement of the extremities due to amniotic bands is detected, Doppler ultrasound is a very important tool. If distal flow is absent, fetoscopy may be necessary; however, if blood flow is decreased but present, release of the band should be considered.

Patients with ADAM complex require a complete pre- and postnatal evaluation supported by karyotype, x-rays of hands and feet, craniofacial CT, as well as the inclusion of a cardiac and renal evaluation in order to arrive at the diagnosis and to make decisions for timely treatment. Hence, knowledge of this entity is imperative by the clinician as well as multidisciplinary involvement of maternal-fetal medicine specialists, neonatologists, geneticists, physicians, neurosurgeons, maxillofacial surgeons, orthopedic surgeons, plastic surgeons and ophthalmologists.

Treatment protocols are based on the presented anomalies from those that endanger the patient’s life or that compromise feeding, growth, function and aesthetics, which are well established individually. ADAM complex remains a very controversial topic. One can clearly see the need for a consensus and explicit pathogenesis and universal diagnostic criteria and classifications. But first, one needs to find and declare the difference of the two entities based on a clinical and epidemiological analysis.\textsuperscript{31}

References

29. Orioli IM, Ribetio MG, Castilla EE. Clinical and epidemiological studies of amniotic deformity, adhesion, and mutilation (ADAM)