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Amniotic Constriction Band: A Multidisciplinary Assessment of Etiology and Clinical Presentation

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Amniotic constriction band, first described in 1832 by Montgomery, is one term used to describe a wide range of associated congenital anomalies, including anular constrictions of multiple extremities, oligodactyly, acrosyndactyly, talipes equinovarus, cleft lip and cleft palate, and hemangiomas. Additional, less common clinical manifestations include complete absence of the limb, short umbilical cord, craniofacial disruptions, neural tube defects, cranial defects, scoliosis, and body-wall defects, such as gastrochisis and extrathoracic heart. Some of these manifestations are uncommonly noted at birth because they result in spontaneous abortion.

The prevalence of amniotic constriction band is approximately one in 1200 to one in 15,000 live births. The prevalence rate for male infants has been reported to be 0.91 and, for female infants, 1.44. These defects are reported to occur 1.76 times more frequently among African-Americans as compared with Caucasians. Evidence of familial involvement is extremely rare. Although temporal and geographic clustering has been reported, this phenomenon is not well understood.

The variability of presentation between patients, the unusual nature of this constellation of findings, and the lack of a consensus on etiology are all reflected in the fact that thirty-four different names have been used to describe this entity in the literature. Most of the descriptive terminology used to describe this entity relates to the extremity manifestations; the central manifestations affecting the face and body have not typically been considered for nomenclature. The various names include amnio rupture sequence, aberrant tissue band syndrome, ADAM (amniotic deformity, adhesions, mutilations) complex, constrictive band syndrome, constriction ring syndrome, amniotic disruption sequence, and Streeter dysplasia, among others.

The use of the word “syndrome” is controversial because there are no classic, consistently present and defining features of amniotic constriction band as are seen in other syndromes. Rayan evaluated the nomenclature and concluded that amniotic constriction band was the most appropriate terminology that is reflective of both etiology and description; we have chosen to employ this same terminology while understanding its limitations related to both etiology and manifestations. The purpose of this review is to describe the clinical presentation of patients with amniotic constriction band and to critically evaluate the various theories of etiology.

Clinical Manifestations

Amniotic constriction band is associated with three general types of anomalies: disruptions, deformations, and malformations. Consideration of the manifestations of amniotic constriction band in this context is helpful both for discussion and for assessing theories of etiology. Disruptions are the breakdown of normal tissue from any cause. No two affected fetuses with tissue disruption will have exactly the same features, and there is no single feature that consistently occurs.

The classic disruptive findings in amniotic constriction band are constrictions, amputations, and acrosyndactyly. Deformations result from abnormal forces on an otherwise normal fetus. Classically, and not simply in amniotic constriction band, deformations may result from oligohydramnios, associated with a resultant direct pressure phenomenon and decreased fetal movement. Talipes equinovarus, scoliosis, and various joint contractures may result. An insult early in gestation results in malformation, or abnormal development, of an organ. Classic malformations associated with amniotic constriction band include body-wall defects, internal organ abnormalities, and craniofacial abnormalities.

There have been several reports of additional anomalies, most of which are consistent with malformations, in patients with amniotic constriction band. In one series, constriction rings were seen together with cleft lip (with or without cleft palate), anal atresia, and ventricular septal defect in 15%, 13%, and 7% of subjects, respectively. If these facial and organ abnormalities are indeed malformations rather than disruptions or deformations, then this study demonstrates either that malformations are associated with amniotic constriction band or that amniotic constriction band anomalies may have more than one etiology.

The classic phenotype of amniotic constriction band includes the involvement of multiple extremities to varying

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degrees and a variety of abnormalities in each patient. The three most common abnormalities include limb or digit amputations, constriction rings, and acrosyndactyly, each of which is discussed below (Figs. 1, 2, and 3). Additional findings may include talipes equinovarus and, less commonly, scoliosis. Even rarer are craniofacial abnormalities, such as cleft lip or cleft palate, body-wall defects, and internal organ abnormalities. These abnormalities require evaluation by specialist physicians in addition to the orthopaedic surgeon, as they may be life-threatening. An evaluation by a clinical geneticist should be performed to comprehensively evaluate the child for uncommon findings and to explore possible etiologies.

There is no widely accepted classification scheme for amniotic constriction band. Patterson classified the common extremity manifestations; this is perhaps the most helpful classification for clinicians. Type 1 includes extremities with simple constriction rings. There may be deficient subcutaneous tissue at the level of the ring, but the extremity distal to the ring is normal. Type 2 is a constriction ring with distal deformity, including atrophy and lymphedema. These findings are thought to represent lymphatic or neurovascular disruption caused by the ring. There may be sensory deficits, especially when rings occur at the proximal aspect of the extremity. Type 3 is acrosyndactyly, or fenestrated syndactyly, which is a distal cutaneous fusion of the skin with separation of the digits proximally. This differs from typical or developmental syndactyly, which results when normal interdigital cell death does not occur during hand development and which always involves the proximal web. Short digits are commonly noted in infants with acrosyndactyly, in contrast to the normal-length digits that are seen in most infants with developmental syndactyly. Finally, Type 4 includes amputation at any level of the extremity or digit.

Three reports of large series of children with amniotic constriction band provide information about the common manifestations of this disorder. There was a high prevalence of prematurity in each study, ranging from 35% to 50%, with an
assortment of other gestational issues, including maternal hemorrhage and amniotic fluid leakage. Two of the three studies demonstrated a greater involvement of the upper extremities, while the third study showed nearly equal involvement of the upper and lower extremities. One of the studies reported an average of three involved extremities. Upper extremities most commonly demonstrated constriction rings, acrosyndactyly, and absence of the terminal aspect of the digit (typically affecting the central digits). Constriction rings were seen at all levels of the extremity. Talipes equinovarus was prominent in all three reports.

Risk factors for amniotic constriction band are not well defined. An epidemiological analysis of a case-control study of birth defects demonstrated that mothers of patients with amniotic constriction band and body-wall defects are more likely to be young and African-American and less likely to be educated, although there were no clear-cut associations with age or race for mothers of patients with limb abnormalities alone. The authors suggested that these differences may indicate different etiologies.

**Body-Wall Defects**

Body-wall defects represent a variety of abnormalities of the ventral body wall; while their exact etiology is unknown, these defects likely represent disruptions or malformations. Body-wall defects have been considered a severe manifestation of amniotic constriction band on the basis of the presumption that body-wall defects represent an earlier rupture of the amniotic sac and/or a more severe presentation than isolated limb abnormalities do. The relationship between body-wall defects and the extremity findings of amniotic constriction band has been established solely through a common presentation in patients, as noted below. Definitive evidence of a causal relationship is lacking.

In one series of twenty-five fetuses with limb and body-wall defects, while 95% of the fetuses had limb defects, “the majority . . . were not typical of ‘amniotic bands’ but nevertheless appeared disruptive in nature . . . .” Less than half (ten of twenty-five fetuses) actually had amniotic bands of any variety. In another review, fifty-four subjects with limb and body-wall defects and a variety of internal organ anomalies were reported as having lower-limb lesions (amelia in seven subjects; limb hypoplasia in five; rotational abnormality in three; split foot in two; and a complex defect in one), but no upper-extremity abnormalities were reported. On the basis of a series of eighteen fetuses with amniotic constriction band, twelve of whom were also diagnosed with limb and body-wall defects, the authors noted that the nine amputations in that series were not typical of amniotic constriction band (one amputation involved an absent radius and several involved “rudimentary” arms), and they concluded that amniotic constriction band and limb and body-wall defects were likely from separate etiologies with a phenotype overlap.

If considered to be malformation-type anomalies rather than disruption-type anomalies, craniofacial clefting and se-
Differential Diagnosis

Amniotic constriction band has become a default diagnosis in the child born with limb deficiency. This is, in part, due to the fact that amniotic constriction band may mimic other conditions, especially the ones presenting with limb-reduction defects. The fact that different insults can cause a similar limb abnormality makes the diagnosis of patients with these defects particularly challenging.

In assessing a child with limb abnormalities that are consistent with a diagnosis of amniotic constriction band, specific gestational risk factors must be considered. There are multiple different human teratogens that may affect limb morphogenesis, including thalidomide, warfarin, phenytoin, valproic acid, and cocaine. Phenytoin and several others, including misoprostol, may cause vascular disruption in a limb that had formed normally\textsuperscript{29}. Diagnostic or therapeutic procedures during pregnancy, such as chorionic villi sampling and dilatation and curettage, can also cause vascular disruption and result in limb abnormalities\textsuperscript{30}.

Ideally, before making the diagnosis of amniotic constriction band, the geneticist constructs a three-generation family tree, with a detailed inquiry regarding limb defects and other potentially associated anomalies, and obtains a detailed history of the pregnancy from five to eleven weeks of gestation, including such issues as drug exposure, trauma, and invasive procedures. Physical examination of the infant at the time of delivery is very helpful; if fibrous bands are attached to the affected limb at delivery, the diagnosis of amniotic constriction band may be made with greater confidence. Unfortunately, this level of detailed information is rarely available.

Syrmbbranchyductyl is commonly misdiagnosed as amniotic constriction band. While both disorders can affect the extremity at the level of the forearm, wrist, or hand, several features distinguish these diagnoses. First, sylmbbranchyductyl affects only one extremity, whereas amniotic constriction band usually affects multiple extremities. Second, with digit loss or transverse failure of formation associated with syrmbbranchyductyl, the distal end of the extremity typically has nubbins with fingernails and there are invaginations at the end of the stump (representing muscle attachment to the skin)\textsuperscript{31}; these findings are not usually seen in amputations associated with amniotic constriction band. Finally, while syntactically may be present in both abnormalities, it manifests as acrosyntactically in amniotic constriction band and as developmental syntactically, usually short digits, in sylmbbranchyductyl.

Other conditions that should be considered in the differential diagnosis of amniotic constriction band include Adams-Oliver syndrome (autosomal dominant inheritance of heterogeneous defects, including multiple transverse limb or digit deficiencies, a scalp anomaly called cutis aplasia, and cardiac malformations)\textsuperscript{29} and a very rare condition characterized by autosomal dominant inheritance of unilateral distal transverse deficiency with nubbins\textsuperscript{32,33}. Another differential diagnosis is ectrodactyly, ectodermal dysplasia, and cleft lip/palate (EEC) syndrome, an autosomal dominant condition caused by mutations in p63 on 7q21-22 with variable deficiency of the central rays of the hands and feet, cleft lip and/or cleft palate, dry skin with variable hypohidrosis, sparse fair dry hair, hypodontia, and thin brittle nails\textsuperscript{34}.

Recently, several genes causing cleft lip and/or cleft palate have been identified; subjects with these genetic profiles may also have oral or facial fibrous bands. The Van der Woude and poiptetal pterygia syndromes have been associated with the IRF6 mutation. Similar findings are noted in the Hay-Wells syndrome, caused by mutations in p63. Furthermore, p63 mutations are also known to be associated with limb anomalies. Therefore, the finding of cleft lip and/or cleft palate in a patient with amniotic constriction band-like anomalies may represent a previously unrecognized syndrome with a genetic basis\textsuperscript{35}.

The majority of cases of amniotic constriction band are sporadic; therefore, the recurrence risk for this condition seems to be negligible\textsuperscript{36} in contrast to the risk associated with other inherited genetic disorders that can cause clinically similar anomalies with higher recurrence risk, such as EEC syndrome. This highlights the importance of establishing the diagnosis of amniotic constriction band.

Etiology

The debate on the etiology of amniotic constriction band has been waged in the literature for the last eighty years with no firm conclusions. Each theory has limitations; some explain certain findings in a convincing fashion while others may provide a more acceptable generalized explanation but inadequately explain specific abnormalities. As the debate has continued, some authors have begun to accept the idea that no single theory can explain all possible manifestations\textsuperscript{27,37}. We will summarize and evaluate the various theories (intrinsic, extrinsic, vascular, and others), with respect to extremity abnormalities (constriction rings, acrosyntactyly, and amputation) and central abnormalities (craniofacial and body-wall abnormalities).

Intrinsic Theory

The intrinsic theory, as described by Streeter in 1930\textsuperscript{38}, holds that an intrinsic, germline developmental abnormality is responsible for the development of amniotic con-
striction band. This theory is often used to explain major craniofacial abnormalities, body-wall defects, and internal organ abnormalities. While other theories may be more convincing in their ability to explain the extremity abnormalities, the intrinsic theory remains a popular means of explaining the central abnormalities.

Bamforth found support for the intrinsic theory in five previous comprehensive investigations on body-wall defects. He concluded that a discrete lesion could cause multiple limb and body-wall defects if it occurred at twenty-six days after fertilization and that the typical “pattern of defects bear more resemblance to the embryonic proximity of the affected structures than to their proximity in the mature body pattern.” This suggests, of course, that other theories that attempt to explain the body-wall defects through a pressure phenomenon or through amniotic band–related pressure are inaccurate. Bamforth does not suggest, however, that this single theory explains all findings of amniotic constriction band.

An evaluation of four fetuses that had limb and body-wall malformations showed that three had internal organ abnormalities and two had separation of the amnion and chorionic cavities; however, the timing of the amnion rupture in each fetus was later than the timing that would explain the malformations that were present in these fetuses. These authors believed that these findings were most suggestive of a germine defect; they dismissed the vascular and banding theories.

The exact nature of a germline defect that may lead to amniotic constriction band is unknown and could be multifactorial. A teratogenic insult that damages germine cells has been proposed, but there is little evidence to support this theory. One report relates the ingestion of misoprostol at nine weeks gestation to a nonviable fetus with an amniotic constriction band-like presentation of upper-limb amputation, bilateral talipes equinovarus, and cerebellar atrophy. The authors of this report did not conclude that there was a definitive link and acknowledged that the defect may have been the result of premature rupture of the amnion.

There are several important critiques of the intrinsic theory. First, this theory does not sufficiently explain the development of banding abnormalities. The argument for a mechanical etiology of the band–related abnormalities is more convincing, as noted below. Second, a germine defect, affecting a defined portion of the developing embryo, would be expected to lead to a more reproducible abnormality. However, children with amniotic constriction band and body-wall defects have a combination of abnormalities that is unique to each child. By this rationale, a disruptive etiology may have more credence than the malformation concept. Finally, as Kino states, “if this syndrome arose from abnormal constitution of the germ plasm, neither fenestrated syndactyly nor constriction rings could possibly result.”

**Extrinsic Theory**

**Background**

The developing embryo sits within two cavities: the inner amniotic cavity, and the outer chorionic cavity. The amniotic cavity (lined by embryonic ectoderm cells) gradually expands and, by twelve weeks, the outer chorionic space is obliterated. It has been suggested that if this space does not undergo obliteration, the chorion does not support the amnion and the amniotic sac may rupture. If the amniotic sac ruptures, amniotic fluid may be lost and the fetus may pass in part or in total into the chorionic cavity; amniotic bands potentially occur as the result of premature rupture of the amniotic sac, and bands and fragments from torn amnion together with mesodermic fibrous strings (which form on both the outer surface of the amniotic membrane and the inner surface of the chorion) may encircle various fetal parts. The amniotic bands are composed of either acellular fibrous tissue or fibrous tissue containing fibroblasts covered by squamous cells. The fibrous nature of these amniotic bands makes them inelastic and produces a ligature effect.

**The Theory**

The extrinsic theory, as described by Torpin in 1965, holds that a rupture of the amniotic sac leads to the formation of amnion chorionic mesodermal bands leading to the development of amniotic constriction band. Torpin reviewed only three cases and discussed a total of eleven, arguing that the asymmetry of the digital amputations and other findings, and the associations with constriction rings and clubfoot, point away from a genetic or an intrinsic cause. The etiology of such findings as limb and body-wall defects and craniofacial abnormalities was not discussed. The cause of early amniotic rupture remains unknown, although trauma has been reported in a few cases.

The gestational age at which the amniotic sac ruptures is believed to be the major factor determining the range and severity of amniotic constriction-band deformities. The rupture can occur at any time during gestation; however, it most likely occurs before twelve weeks. Theoretically, early rupture could decrease amniotic fluid, causing the compressive consequences of early constraint, such as scoliosis and clubfoot. Additionally, and more severely, a vascular disruption could result from the early rupture, leading to facial clefts and limb reduction with body-wall defects.

An examination of eighteen stillborn fetuses with amniotic constriction band revealed that eleven had bands comprised of amniotic epithelium encircling one or more limbs. In two fetuses, the bands encircled the umbilical cords, a known cause of fetal death. The authors concluded that “incomplete amniochorionic fusion with partial persistence of the extra embryonic coelom explains the accidental character of most cases … .” In contrast to Torpin’s assertion that the bands are mesodermal, the bands examined in this study consisted of amnion. The authors also described another lesion—the broad amniotic adhesion—as being the result of a distinct pathological process. They believed that raw surfaces resulting from “fetal defects associated with the disruption of the ectodermal integrity” were responsible for facial abnormalities. They could not relate limb and body-wall defects to the extrinsic theory and thought these were a separate entity entirely.
An evaluation of seventy-nine patients with amniotic constriction band, including banding and/or major deficiencies, resulted in the conclusion that the timing of the amnion rupture and the nature of the entanglement and subsequent banding determine the pattern of presentation. Later rupture primarily affects the limbs, whereas earlier rupture can lead to multiple malformations and limb and body-wall defects. Another review of twenty-seven cases of limb and body-wall defects resulted in the conclusion that these represent the most severe manifestation of early amnion rupture; amniotic bands were noted in 41% of these subjects. The authors concluded that, according to the extrinsic theory, early amnion rupture (and resulting loss of amniotic fluid and subsequent pressure phenomenon) causes the severe “non band-related defects in limb/body wall deficiency.” They also cited animal studies (see below) supporting the crucial nature of sufficient amniotic fluid to normal development, and concluded that defects depend on the timing and extent of the amnion rupture, the extent of compression, and the presence or absence of banding.

Others have performed amniotic sac puncture in rats and found that this caused hemorrhagic lesions, tissue necrosis, limb reduction, and cephalic changes. They attributed these findings to intrauterine compression related to lost amniotic fluid and uterine pressure and subsequent obstruction of circulation.

Do Tight Bands Cause Constriction Rings? Scientific investigations including animal and human studies have supported the extrinsic theory. In one study, researchers used silk ligature to simulate amniotic bands in forty rats. In Group 1, the limb was placed through the amniotic sac and uterine wall and the uterus was allowed to constrict around the limb. In Groups 2 through 4, the limbs were exteriorized through a small hysterotomy and a single suture was tied around the extremity prior to placing the limb back into the uterus and closing the hysterotomy. Group 2 had a loose ligature; in Group 3, it was tight proximally; and, in Group 4, it was tight distally. Late examination in Group 1 demonstrated classic constriction rings with changes distally. Group 2 had constriction rings without distal edema. In Group 3, 40% of the rats died but all survivors had rings with infarction distally. Finally, in Group 4, nine of the ten had deep rings and distal infarction.

Other investigations with similar findings include animal and human studies of fetoscopy. In a fetal lamb model, a constrictive band was applied at 100 days gestation, and typical amniotic constriction-band findings were demonstrated at birth, including distal deformity, pitting edema, and venous congestion. Much milder findings with a near normal limb appearance were noted when the band was released fetoscopically twenty-five days later. Others reported fetoscopic release at approximately twenty weeks gestation in humans, with improvement in the appearance of the extremities. These reports do not advocate isolated fetoscopic release, as the risks of such intervention are high. However, these investigations lend credence to the concept of a defined band causing the extremity manifestations of amniotic constriction band.

Prenatal ultrasound examination of one subject resulted in the detection of constriction rings at twenty-one weeks gestation, with a subsequent loss of blood flow and amputations; the authors concluded that this case supported the extrinsic theory. Other ultrasound investigations have also provided similar findings in the upper extremity. At birth, constriction of the arm with band formation was noted after the insertion of a soft and flexible pleuro-amniotic shunt into a twenty-three-week-old fetus, providing evidence that a compressive band can cause constriction bands in humans.

Critique of Extrinsic Theory

There are several important limitations to the extrinsic theory. First, the internal visceral abnormalities and limb and body-wall defects are difficult to explain by the concept of band-applied pressure. Facial anomalies, such as cleft lip or cleft palate, are also difficult to explain by the extrinsic theory, although band pressure has been argued to cause such defects. Oligohydramnios from an early amnion rupture has been cited as a link between banding and these more severe deficiencies. The consequences of very early amnion rupture may include compressive consequences of early constraint, such as scoliosis and clubfoot, as well as vascular disruption leading to facial clefts and limb reduction with body-wall defects. Yet it is difficult to understand how the array of limb and body-wall findings could be caused by pressure on one area of the fetus.

Second, this theory depends in part on the concept of amnion rupture leading to decreased amniotic fluid. However, despite some reports of amniotic fluid leakage, oligohydramnios is not consistently noted and the presence of the chorion may prevent amnion rupture from causing oligohydramnios.

Vascular Theory

Van Allen suggested that vascular disruption can lead to both internal and external defects. In her report of twenty-five children with limb and body-wall defects, twenty-four had a limb deficiency, twenty-four had internal organ abnormalities, eighteen had a cephalic deficit, fourteen had craniofacial defects, and ten had amniotic bands. The author related the various abnormalities, especially the internal organ deficiency, to vascular disruption causing a systemic alteration of the embryonic blood supply. The author theorized that a traumatic event, such as amnion rupture, amniocentesis, direct trauma, or exposure to a teratogen at four to six weeks of gestation, may disrupt development by interrupting the blood supply to the fetus, causing hemorrhagic necrosis and embryonic circulatory collapse. The timing of the insult determines the presenting abnormality.

A similar theory, based on the effects of uterine blood-flow disruption in rat embryos, was tested in a study designed to replicate the effects of maternal uterine trauma. Amputation and digit hypoplasia resulted; constrictions were seen but were not particularly common.
Another theory of vascular disruption holds that a specific intrauterine traumatic event, as may be simulated in an animal model by an intra-adnexal injection of glucose, leads to the development of amniotic constriction band. In this rabbit experiment, injections into the uterine adnexa performed between eleven and twenty days of gestation (corresponding to two to three months in humans) led to cellular destruction and hemorrhage, causing amniotic constriction band-like transverse limb amputations at different levels and facial anomalies, including cleft lip, ulcers, tarsal anomalies, and clubfoot. Amniotic bands, not previously produced in a laboratory setting, were infrequent. The authors concluded that neither amniotic sac rupture nor amniotic bands play a role in human disease.

A rat amniocentesis study demonstrated that hemorrhage preceded limb constriction, amputation, talipes equinovarus, and cleft palate. Early amniocentesis caused a higher rate of both limb malformation and cleft palate and was more lethal than amniocentesis performed later. There are no strong data suggesting that amniocentesis in humans leads to amniotic constriction band, but reduction defects similar to amniotic constriction band have been documented after chorionic villus sampling.

Critique of Vascular Theory

Bamforth evaluated the vascular hypothesis in terms of embryonic organization and did not find this theory credible as he did not believe that the abnormalities followed the known embryonic vascular patterns. He believed that the embryonic anatomical proximity was more “striking” than the vascular relationships.

Other Theories

None of the above theories can explain all findings in patients with amniotic constriction band, especially the nonextremity findings. Ds (short for “disorganization”) is an autosomal dominant mouse mutant that produces a wide variety of birth defects with markedly reduced penetration; it has been suggested as a model for an amniotic constriction band-like phenotype. The Ds gene has yet to be identified, but much has been inferred through murine breeding studies. This gene is a candidate for the intrinsic factor proposed by Streeter.

Conclusions

Based on an assimilation of historical and current research, the findings in amniotic constriction band can be grouped as classic, which can be explained by disruptions and deformations (constriction rings, amputation defects, and talipes equinovarus), and nonclassic, which result from malformations (cleft lip and/or cleft palate, imperforate anus, and body-wall defects). These two groups of findings have different etiologies that cannot be reconciled on the basis of our current understanding. The phenotypic overlap between classic and nonclassic findings in amniotic constriction band confounds scientists and clinicians, and the search for a unifying theory of causation continues.

References