Epidemiology and risk factors of amniotic band syndrome, or ADAM sequence

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Summary

Amniotic band sequence (ABS) is the term applied to a wide range of congenital anomalies, most typically limb and digital amputations and constriction rings, that occur in association with fibrous bands (1). These alterations may be associated or not with cutaneous and visceral abnormalities.
This work, which is a literature review, examines several studies that relate to cases of amniotic band syndrome (SBA). In particular, our attention was focused on the causes and pathogenesis of the SBA. These for the most part are still unknown, but from what we observe in different jobs, are due to a mechanism of vascular damage. Therefore in this paper we examine chemical risk factors, like smoking, drug use, maternal hyperglycemia, mechanical risk factors such as the puncture of the amniotic sac after amniocentesis. We also speak of the altitude as a risk factor related to blood pressure, of the increased incidence of disease in primigravid, in women with a low level of education, in which the pregnancy was not planned, and then we talk of a higher incidence in young fathers and of the role of familiarity.

Key words: digital amputation, constriction rings, vascular damage, chemical risk factors, mechanical risk factors, familiarity.

Introduction

Amniotic deformity, adhesion, and mutilation (ADAM) sequence, acronym used by Hermann and Opitz in the 1974 is a heterogeneous condition, with a broad spectrum of anomalies, where intrinsic causes, as defect of germ plasm (2), vascular disruption (3) and disturbance of threshold boundaries of morphogens during early gastrulation, alternate with extrinsic causes as amniotic band rupture to explain the condition.
One affected infant in every 11,200 births, was found with stable trends during the last 17 years (4).

Materials and methods

We searched from to PubMed articles of studies concerning the epidemiology and above all the risk factors of amniotic band syndrome, using as keywords for the search "amniotic bands" and "amniotic band syndrome." We used for this study only those items for which we have found the text in full, for a total of 10. The articles are all based on recent studies from 2005 and 2010. The oldest item that we have used is on a study carried out in the year 2000.

Etiopathogenetic theories

There are two main theories for the pathogenesis of ABS, and are referred to as the ''extrinsic model'' and the ''intrinsic model.'' The intrinsic model was proposed by Streeter in the 1930 (5) and suggests that the anomalies and the fibrous bands have a common origin, caused by a perturbation of developing germinal disc of the early embryo. Later, the Torpin's model of the 1965 (6), the "extrinsic theory", suggested that the birth defects are caused by the action of the fibrous amniotic bands with the sequence rupture of the amnion, followed by loss of amniotic fluid and extrusion of all or parts of the fetus into the chorionic cavity. The fetus' limbs, while trapped there are subjected to vascular compression and then necrosis.
This mechanism, today the more accepted theory, as some authors believe (7) cannot explain other types of defects associated such as imperforated anus, polydactyly (8), septo-optic dysplasia (9) and Cleft lip with or without palat (CLP) (10).These authors therefore suggest, that at least part of the cases of abs have a genetic basis.
Other authors believe that these anomalies can be explained, however, by the theory of extrinsic. In the past two decades, several reports provided evidence that vascular compromise may be the underlying cause of the craniofacial and abdominal wall defects (11-14).
It is not clear if amniotic bands are the primary cause of or are secondary to vascular disruption. If amniotic bands are secondary to vascular disruption, then a shared patho-

genesis for each case group might be exhibited by similar risk factors.

A variety of congenital anomalies are thought to result, at least in some instances, from a vascular disruptive process during gestation, including gastroschisis, small intestinal atresia, terminal transverse limb reduction defects, renal agenesis, microtia, clubfoot (15), and even the same Septo-optic dysplasia (16). These defects that are accompanied by the presence of so-called 'amniotic bands' – presumably fibrous tissue that originated in the amniotic lining – have also been attributed to vascular disruption (17,18). An example in support of this is the existence in the literature of the association between the Septo-optic dysplasia and the syndrome of amniotic bands, two disorders involving structures of body totally different. Septo-optic dysplasia (SOD) is a heterogeneous disorder characterized by at least two of the following features: absence of the septum pellucidum, optic nerve hypoplasia, and pituitary gland dysfunction. While most cases represent an isolated defect, Septo-optic dysplasia has also been seen in association with mutations in single genes, as a part of multiple congenital anomaly syndromes and with exposure to various teratogens. In literature there are cases of Septo-optic dysplasia where in addition to brain defects are described limb defects suggestive of amniotic bands. These cases suggest a vascular pathogenesis of Septo-optic dysplasia in some individuals. This hypothesis is also supported by the sporadic occurrence of Septo-optic dysplasia and its association with neuropathologic findings suggestive of vascular insults, decreased maternal age and vascular teratogens, that as we will see later appear to be risk factors for ABS.

Another important clinical association is the presence in some patients of limb reduction defects and cleft palate (CLP). Mutations of genes involved in cleft lip and cleft palate are known. This could be the basis for a better understanding of the genes involved in the amniotic band syndrome. It is interesting to note that several of the recently identified cleft lip and palate genes have oral or facial fibrous bands as one component finding. These include van der Woude and popliteal pterygia syndrome, caused by mutations in IRF6 (19, 20), and Hay Wells Syndrome, caused by mutations in p63 (21). Furthermore, p63 mutations are also associated with limb anomalies (22). May be that cases with ABS-like anomalies associated with CLP represent a different condition, possibly caused by mutations in the genes Disorganization, p63, or IRF6. Finally, in the literature there are reports of patients with Amniotic band syndrome and Cleft lip and palate, which have additional anomalies, such us supernumerary left nipple, polydactyly, vertebral segmentation defects, imperforate anus, and renal agenesis, and a skin papilla. Donnai and Winter (1989) concluded that these cases represented the human homolog of a gene studied in mice whose mutation is due to similar disorders (Ds). The Ds gene has yet to be identified, but much has been inferred through murine breeding studies. It is a gain-of function mutation that causes malformations through a two hit mechanism (23).

Clinical evidences of a vascular pathogenic mechanism

The pathogenetic mechanism underlying the amniotic band syndrome (SBA) would indeed be a mechanism of vascular compromise as evidenced by a prospective study that was conducted by the Department of Plastic and reconstructive Surgery Nelson R Mandela School of Medicin (University of Kwazulu-Natal, Durban, South Africa).

In this study, were observed using RMA (magnetic resonance angiography) and TCA (TAC angiography) in children born alive, limbs affected by amniotic bands. Vessel abnormalities were found in the limbs affected such as "bifurcation or trifurcation of the popliteal artery or a very attenuated segment of the SFA with no discernable branches of the popliteal artery". These abnormalities were absent in the healthy contralateral limbs (24). Other vascular abnormalities in the affected limbs included absent major vessels, atretic segments in the major limb arteries and absent branches. Some branches of the trifurcation petered out above the band.

Epidemiology

The prevalence of the syndrome varies in different studies. According to data from a study on the Latin American population the birth prevalence rate of ADAM sequence was 0.89 per 10,000 births (95% CI: 0.75-1.03) or 1:11.200 births. Epidemiologic analyses were done over the 1982-1998 period, including live births and stillbirths. The annual rates were homogeneous. Other studies have found a different prevalence of disease in the population. Some have found a prevalence of less than 1:18.000 which did not include the subgroup with defects of the trunk and abdominal wall, called LBW (LBW or BWC is one syndrome that includes presence of body wall defects with evisceration of thoracic and/or abdominal organs, limb deficiency, and myelocystocele) (25).

Other more prevalent 1:1.200 (26). Probably this higher prevalence found by Ossipoff and Hall was related to the miscarriages, stillborns, and newborns inclusion.

The prevalence at birth was homogeneous among 10 of the 11 analyzed Latin American countries but not for Bolivia, where the birth prevalence rate was twofold higher. The observed geographic difference in birth prevalence could be a useful indication to study specific genetic and environmental candidate factors populations (27).

Supposed risk Factors

A Latin American study on congenital malformations has shown that there was an excess of cases of SBA in populations living at high altitude (28).

A hypoxia mechanism derived from high altitude could be involved in the etiopathogenesis of some ADAM cases and the other described defects. Another explanation could be ethnicity, since Bolivian population studied here are mainly from Amerindian extraction (29).

According to the results of this study there was a familial occurrence of the syndrome. The risk of ADAM sequence was 42.8 times higher among the first-degree relatives, and 50.8 times higher among the second degree relatives than the risk in the general population (0.0000894) (30). Cases with ADAM sequence were more firstborn than controls (OR: 2.16; CI: 1.25-3.72); there were more acute illness (OR: 2.00; CI: 1.08-3.72), medication drug use (OR: 2.38; CI: 1.32-4.26), in three of these cases misoprostol was the drug responsible, and vaginal bleeding

(OR: 2.00; CI: 1.00-4.00) during the first trimester of pregnancy among cases than controls. Birth weight lower than 2,500 g was in excess among cases (OR: 5.55; CI: 2.92-10.54), which could be explained by intrauterine growth retardation (OR: 4.25; CI: 1.43-12.63), as well as by prematurity (OR: 4.86; CI: 2.15-10.96).
Non-cephalic fetal presentation was also more frequent among cases than controls (OR: 2.33; CI: 1.07-5.09).
A case-control study carried out on metropolitan areas of Boston, Philadelphia and Toronto concluded that ARS (amnion rupture sequence) and BWC (presence of body wall defects with evisceration of thoracic and/or abdominal organs, limb deficiency, and myelocystocele) are two different disease entities, based on different epidemiological and etiological factors. This study collected epidemiological data from 1976 to 1998. There were 73 cases with ARS and 11 with BWC.
ARS cases were further subdivided according to affected structures: there were 53 with only limbs affected (ARS-L) and 20 with non limb defects with or without limb defects (ARS-NL).
Risk estimates tended to be similar for ARS-L and ARS-NL cases but different for BWC cases, suggesting different etiologies. Parity was the one exception to this pattern, where ARS-NL and BWC case mothers had similar histories. Parity was not a statistically significant risk factor, but the observed approximate twofold increases in risk of ARS-NL and BWC for a first birth suggest it may be important. Why first birth in and of itself would be related to these defects is not clear, but the vascularity of a multigravid uterus is likely to be different than that of a primigravid uterus.
Data from the study of Boston suggest that young maternal age, low maternal education, unplanned pregnancy, and non-white/non-Hispanic race/ethnicity might increase the risk of BWC in offspring. It is not clear if the reduced risks for white non-Hispanic offspring were due to socioeconomic status (beyond differences in maternal age and education) or whether there might be a genetic basis.
The same study estimated the ARS does not recognize these conditions as risk factors.
A Hungarian study examined isolated amniogenic limb defects (equivalent to ARS-L) and reported no association for maternal age (31), similar to what observed in the first study (32).
In contrast to those and findings of the American study, the Hungarian study found multiparous women had a greater risk association for maternal age (33). The Hungarian study also reported positive associations for low socioeconomic status, unplanned pregnancy, and smoking during pregnancy in relation to ARS-L, contrary to findings of the American study for that defect. In reality, the Hungarian study has some limitations. ARS and BWC diagnoses were determined by medical record reports and study investigators did not separately confirm them by examination of the baby or placenta. Since difficulties in accurate diagnosis and classification of ARS and BWC diagnoses are well recognized, there is a real possibility of misclassification.
Cigarette smoking during early pregnancy is vasoconstrictive and has been related to gastroschisis, which is thought to arise from vascular disruption (34-36). However, maternal smoking was not found to be associated with ARS or BWC in the American study.
Acetaminophen is one of the most commonly used medications during pregnancy (37). The American study observed that use of acetaminophen in early pregnancy was associated with increased risks of ARS cases but not BWC cases. Acetaminophen is not known to be vasoactive, but it has been associated with a slight increase in gastroschisis risk in two studies (38,39).
Increased risks for acetaminophen use should be interpreted with caution because they may be confounded by indication for use (40). In particular, there may be confounding by fever as acetaminophen is an antipyretic and hyperthermia has been implicated as a vascular disruptor (41).
There is a Californian study according to which young paternal age, i.e., less than 29 years, was associated with an increased risk of amniotic bands (OR: 0.87 [0.78, 0.97]).
This study examined the association between paternal age and a wide range of structural birth defects. Younger paternal age, was associated with a higher risk of amniotic bands, pyloric stenosis, and anomalies of the great veins, with the risk decreasing between 7 and 13% for every 5-year increase in father's age (42).
There is, however, no clear biological mechanism for the association between younger paternal age and birth defects. The increase in risk observed among younger fathers in our study could be attributable to an interaction of genetic factors with behavioral factors such as the use of alcohol and recreational drugs (43).
Data were drawn from The California Birth Defects Monitoring Program, a population-based active surveillance system for collecting information on infants and fetuses with defects born between 1989 and 2002. In the aforementioned research, however, there is a lack of consistency across studies with respect to the source of data on birth defects, the range of birth defects examined, and the methods for analyzing maternal age.
In a study conducted by the National Center on Birth Defects and Developmental Disabilities (Centers for Disease Control and Prevention, Atlanta, GA) has been observed that Maternal cigarette smoking and aspirin use each increased the risk of AB-L (Limb reduction deficiencies that are accompanied by amniotic bands) (44).
Cases with amniotic bands were also associated with glycaemic intake, but unlike anorectal defects and neural tube defects (NTDs), which were seen to be associated particularly maternal obesity, the effect appeared to be confined to carbohydrate quality (dietary glycemic index). One study with only 12 amniotic band cases reported no association with obesity (45).
Several workers have been able to produce experimentally typical amputations, cranial malformations, and syndactylies, even in the absence of band formation, with amniocentesis (46,47) amnioreduction or septostomy in twins. They noted vascular changes, and hemorrhage or hematoma as the primary event. In some cases, secondary adhesions to the amnion could exist (48).
It also described a case of monochorionic biamniotic twin pregnancy submitted to selective fetoscopic laser photocoagulation for twin-to-twin transfusion syndrome at 16 weeks of gestation. The procedure was complicated by the death of one of the fetuses at 24 weeks of gestation. Moreover, the surviving twin was diagnosed postnatally with pseudoamniotic band syndrome, presenting with affected limbs. The incidence and risk factors for Pseudoamniotic band syndrome (PABS) after fetoscopy-guided laser have not been documented (49).

Conclusions

The amniotic band syndrome is a heterogeneous disease which comprises clinical pictures very different, which may affect only the limbs, or the ends of the same with amputation, but also the abdominal wall as in the cases of the syndrome associated with gastroschisis or omphalocele. It may be associated with congenital malformations such as cleft lip and palate (CLP), micrognathia, club foot, or more complex syndromes like Patau Syndrome or Septal Optic Dysplasia. The association of limb reduction defects and malformations involving different organs and different devices, supports the " intrinsic model". According to this theory, in fact, the ABS would be the result of a vascular insult, which occurs very early in the embryogenesis. Many syndromes with malformations that are associated in the literature with ABS, as the septum optic dysplasia and cleft lip and palate, share vascular risk factors with the amniotic band syndrome. Surely genetic predisposing factors are involved, as can be inferred by the higher incidence of the syndrome in first degree relatives of the affected individuals. No less important, however, appear to be acquired yearly factors, such as the use of drugs, tobacco, diabetes, known for their action on the vascular system or even iatrogenic factors like the sting from amniocentesis which are an insult to the amniotic membranes. The finding, reported in the literature of iatrogenic cases of amniotic band syndrome, which occurred after amniocentesis or amnioreduction could support instead a different pathogenetic mechanism, which is closer to the extrinsic model. We can presume that both models designed to explain the pathogenesis of amniotic band syndrome, the "extrinsic model" and the "intrinsic model" are correct. Presumably, both mechanisms operate, alone or in combination, to determine the syndrome, which is given by a combination of genetic and environmental factors.

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