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Epidemiologic characteristics of amniotic band sequence with limb malformations without body wall defect: data from the Polish Registry of Congenital Malformations

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Abstract

Amniotic Band Sequence (ABS) is a rare disruptive condition, with a variable spectrum of congenital defects caused by fibrous bands emerging as a result of amniotic rupture in the first trimester of gestation. Several factors, such as young parental age, primigravidity, febrile maternal illness, and drug use in the first trimester, were postulated to have substantial influence on ABS prevalence rate. We aimed our study to determine the prevalence of ABS with limb defects, but no body wall affectation, in a Polish population. We also examined the influence of different parental, gestational and environmental factors on the ABS prevalence value, and assessed the rate of gestational complications associated with this disorder. Among 1 706 639 births surveilled between 1998 and 2005, 36 liveborn infants with ABS-L were reported to the Polish Registry of Congenital Malformations, giving a global prevalence for a Polish population of 1 per 47 619 livebirths. We found that young maternal age, young paternal age, and primigravidity significantly increase the risk of ABS-L, when their effect was analyzed independently. However, because of a close relationship of these variables, we analyzed their mutually adjusted effect using conditional logistic regression models, and found that young maternal age proved the strongest risk factor for ABS-L (p = 0.0508). The condition was also more prevalent in infants with low birthweight (OR = 5.71; $p < 0.0001$). Since gestational complications are often relevant to maternal age and birth order, we introduced an adjustment for these variables, and found that respiratory tract infections and vaginal bleeding/spotting convey approximately fourfold increased risk of ABS-L (OR = 3.72/p = 0.0058 and OR = 3.70/p = 0.0014 respectively).

Key words: amniotic bands, epidemiology, limb deformity, limb reduction, congenital defect, risk factor

Introduction

Amniotic Band Sequence (ABS) also known as Amniotic Deformity, Adhesion, and Mutilation (ADAM) complex or Congenital Constriction Band Syndrome (CCBS) is a relatively rare condition. The prevalence of ABS ranges from 1:11 200 in South American population [1] to 1:21 277 in Spanish [2], or even 1:50 579 in North American [3]. Kalousek and Bamforth [4] reported that ABS occurs with very high frequency of 1:56 in previable fetuses, although lower figure was estimated by Orioli et al. [1], at approximately 1:1 855 or 5.39 per 10 000 stillbirths.

The pathogenesis of ABS remains unclear. It has been widely accepted that fibrous bands emerging in the first trimester of gestation as a result of amniotic rupture are the

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primary culprits of infants' congenital defects [5]. However, huge variability of observed anomalies gave rise to numerous hypotheses trying to explain precisely ABS etiopathology [6-17]. Some of the ABS symptoms, such as limb reduction defects, constriction rings, craniofacial clefts or club feet plausibly result from simple mechanical disruption or deformation, caused directly by fibrous bands or streaks that entangle the developing fetal parts [5, 18]. Other structural defects, for example abdominoschisis, thoracoschisis, cardiac and urogenital anomalies, and polydactyly are probably caused by failure in establishment of appropriate morphogenetic boundaries in early embryonic structures (presumably due to amniotic attachment), and thus should be considered as malformations [6, 7].

It has been postulated that several factors may have substantial influence on the ABS prevalence rate. The most frequently proposed are ethnicity, maternal age, order of pregnancy, birth sex, febrile maternal illness/drug use in the first trimester, altitude of inhibition over the sea level [1, 19]. In addition, there is an abundance of epidemiological and clinical data strongly suggesting that ABS with body wall complex (BWC), which is extremely rare, presents a separate entity from more frequent amniotic bands without body wall involvement [2, 20]. Differential characteristics between children belonging to both groups encompass: male to female ratio, mean birth order, mean birthweight, mean gestational age at delivery, or even the pattern of congenital anomalies [2]. Above discrepancies most probably reflect differences in etiopathogenesis of these two ABS entities.

Considering the above findings we aimed our study to determine the prevalence of amniotic band sequence with limb defects, but with no body wall affectation, in a Polish population of approximately 1.7 million liveborn infants. We examined the influence of different parental, gestational and enviromnental factors on its value and assessed whether there is an increased rate of gestational complications associated with this disorder.

Material and methods

Clinical material

The data derive from the Polish Registry of Congenital Malformations (PRCM), a high quality population-based registry, currently monitoring approximately 300 000 births a year in 16 Polish provinces. The PRCM collects information on structural defects, diagnosed before the end of the second year of life. Minor anomalies are excluded from the registry according to the EUROCAT guidelines [21]. The main source of information is a physician-filled registration form. For each child with a congenital anomaly, a detailed description of the congenital malformation is recorded in a computer database. Additional information include the date of birth, birth order, birthweight, gestational age at the delivery, child`s age (or gestational age) at diagnosis, parental age, parental consanguinity, course of pregnancy, risk factors before and during pregnancy (including mother`s diseases, medications and addictions), family history including previous pregnancies, information whether the child was born alive, karyotype, and autopsy examination results. The PRCM methodology has been previously published [22].

Between January 1998 and December 2005, the PRCM surveilled a total population of 1 706 639 consecutive births (1 697 469 liveborn and 9 170 stillborn infants). 42 232 of them had major anomaly/anomalies. During these 8 years, among 9 170 stillborn cases, only one affected by ABS was noted. This reflects underascertainment of this condition among stillbirths. Further epidemiological analyses were thus limited only to livebirths. Throughout the study period, 48 liveborn infants with the diagnosis of amniotic band sequence/congenital constriction band syndrome – code Q79.80 according to ICD-10 [23] were successively reported to PRCM. In 3 cases clinical description was insufficient or missing, therefore we took into consideration only 45 infants, for whom the information on structural defects and course of pregnancy was comprehensive. In addition, in order to obtain a more homogeneous group, following Martinez-Frias suggestions [2, 20], we decided to exclude from the analysis 9 infants with body wall complex. Out of the 36 remaining children, we also ruled out a case of a severly malformed infant, who presented with craniofacial disruptive defect (cleft palate, absent nose, anophthalmos) and encephalocele, with cranial adhesion to placental membranes, and had neither body wall, nor extremity involvement.

In total, we ascertained 35 infants with limb involvement, designated as ABS-L. All children were matching the Patterson`s criteria for congenital ring constriction syndrome [24]. The maternal age, paternal age, birthweight and gestational age were categorized in accordance with the available demographic data from the Polish Central Statistical Office. For each variable we considered only the cases, for whom the PRCM data were unequivocal.

Statistical Methods

The prevalence of ABS-L was calculated as a ratio of ABS-L cases and the overall number of livebirths within the same time interval and area. Demographic data for years 1998-2005 were culled from Demographic Yearbooks of Poland [25]. Chi-square Test was used to assess differences in prevalence by sex and birthweight. To analyze the homogeneity of prevalence figures by years, we used Fisher-Freemann-Halton correction of the Chi-square Test. The analysis of the influence of parental age on the ABS-L prevalence was performed in two stages. First, we examined the effects of maternal and paternal age individually, with reference to demographic data using logistic regression model. In the second stage, since both variables are tightly interrelated, we analyzed their mutually adjusted influence on ABS-L prevalence using conditional logistic regression model. We created 2 specific control groups selected by random-digit dialing from the control database comprised of 4 750 liveborn children with no major congenital anomaly recognizable at birth. Control cases were born in years 2004-2005 in the PRCM area. Information on

gestational complications from control mothers was collected during the first week following pregnancy confinement. First control group was matched by maternal age with case:control ratio of 1:15 (total of 525 controls). This group was used to develop conditional logistic regression model to examine independent effect of paternal age adjusted for maternal age. Analogous statistical model and control group, consisting of 480 controls (since in 3 cases the information on father's age was missing), was created to study the effect of maternal age adjusted for paternal age.

The initial analysis of the effect of birth order on the prevalence of ABS-L was performed with a Chi-square Test in relation to demographic data. Next, with the use of maternal age matched controls, we developed a multivariable conditional logistic regression model, including birth order and complications of pregnancy, to eliminate errors that could result from interrelation of all variables.

Statistical analyses were performed using StatXact-3 version 3.0, Cytel Software Corporation (Fisher-Freemann-Halton Test), Statistica version 8.0, StatSoft (Chi-square Test, logistic regression), and R version 2.6.1 (conditional logistic regression). Type I error rate of 0.05 was used as a cut off value to declare statistical significance.

Results

Table 1 presents global and annual prevalence rates of ABS-L for liveborn infants delivered between 1998 and 2005. No statistically significant annual fluctuation in the occurrence of ABS-L was observed throughout the study period. We obtained global prevalence of 0.21 per 10 000 livebirths (1:47 619).

Table 1. Prevalence of ABS-L by years among liveborn infants

Year	ABS-L	Births	Prevalence
1998	2	158026	0.13
1999	1	160443	0.06
2000	3	157989	0.19
2001	3	196131	0.15
2002	5	229863	0.22
2003	10	228487	0.44
2004	8	279714	0.29
2005	3	286816	0.10
Total	35	1697469	0.21

p-value = 0.2536
(Fisher-Freemann-Halton correction of Chi-square Test)

Table 2 depicts the frequency of ABS-L with reference to maternal age at delivery. Mean age of mothers of affected children was 24.9 years. 11 infants (31.4%) were born to very young mothers – aged 21 or less. In addition to this, the majority – 33 out of 35 cases (94.3%) – were born to mothers under the age of 30. Thus, prevalence rate for this subgroup reached 0.27. In mothers aged 30 or more the prevalence rate was lower with value of 0.13. Logistic regression model showed that the risk of having affected child decreases gradually by 33% with an increase of one range unit (5 years) of maternal age (OR = 0.67; 95% CI [0.45-1.01]).

Table 3 analyzes prevalence rates in different fathers' age groups. Mean paternal age was 26.7 years with similar to maternal age effect of this variable on the prevalence of ABS-L (OR = 0.63; 95% CI [0.44-0.92]).

In the second stage of calculations, we entered both parental age variables simultaneously into the conditional logistic regression model. Maternal age adjusted for paternal age was borderline significant (p-value = 0.0508), whereas paternal age adjusted for maternal age was far from reaching statistical significance (p-value = 0.128).

As shown in table 4, about 70% of the ABS-L infants were born from the first pregnancy, whereas this proportion for general population was 50%. The predilection of primigravidity in ABS-L was statistically significant when considered in isolation with maternal and paternal age. However, adjusted for maternal age, primigravidity turned out to have no major impact on ABS-L prevalence (p-value = 0.494).

ABS-L affects predominantly infants with low birthweight (< 2500 g) and is approximately 6 times less frequent ($p < 0.0001$) among children with normal weight at birth (Table 5). Mean birthweight for males, as well as females, was placed within the range from 25th to 50th percentile. Mean gestational age at confinement in analyzed sample was 36.7 weeks.

Table 6 puts forward prevalence by sex and sex ratio in infants with the diagnosis of ABS-L. We observed slightly higher proportion of males (62.9%) compared to females (37.1%), but the difference failed to reach statistical significance (P = 0.18), most likely due to a small sample size.

Table 7 presents the incidence of gestational complications with adjustment for maternal age and birth order, since these variables are highly interrelated with one another and cannot be considered separately. In ABS-L cases we observed considerably higher frequency of vaginal bleeding and/or spotting and upper and/or lower airway infections.

Discussion

The prevalence of ABS-L in a Polish population of liveborn infants was estimated to be 0.21 (1:47 619), and is lower than its counterparts for total births published by Martinez-Frias[2] for a Spanish population (0.47 or 1:21 277), or by Orioli et al. [1] for South American population (0.89 or 1:11 200). On the other hand, it is concordant with the data from British Columbia Health Suveillance Registry for North American population (0.19 or 1:50 579 in years 1952-1984 for livebirths) [3], and with the EUROCAT data, accrued from different European registers. Mean prevalence of ABS as a whole (including BWC) for live births in European population in years 1980-2005 was 0.18 [26]. ABS-L seems to occur with notably higher frequency in South American population compared with European or North American. This divergence may indicate

the existence of yet unidentified ancestral or environmental factors, having substantial influence on the prevalence value.

It has been previously suggested that several factors may affect the prevalence of ABS-L. According to the study by Orioli et al. [1] primigravidity and high altitude of inhabitance (>2000 m over sea level), considerably increase the risk of ABS, whereas maternal age, paternal age, parental educational and socio-economic status, parental consanguinity, ethnicity, multigravidity and preceding abortions had no statistically

Table 2. Maternal age and prevalence of ABS-L

Maternal age at birth	ABS-L (N = 35)	Demographic data (N = 1697469)	Prevalence (N = 0.21)
≤24	15	650908	0.23
25-29	18	590533	0.30
30-34	1	301492	0.03
35-39	1	121200	0.08
≥40	0	33336	0.00

p-value = 0.0496 (Chi-square Test)

Table 3. Paternal age and prevalence of ABS-L

Paternal age at birth	ABS-L (N = 32)	Demographic data (N = 1605886)	Prevalence (N = 0.20)
≤24	8	315670	0.25
25-29	16	583093	0.27
30-34	8	397516	0.20
35-39	0	191722	0.00
≥40	0	117885	0.00

p-value = 0.0135 (Chi-square Test)

Table 4. Primigravidity in ABS-L infants

Order of pregnancy	ABS-L (N = 35)	Demographic data (N = 1697469)	OR [95% CI]
1st	25 (71.4%)	841552 (49.6%)	2.54 [1.22-5.30]
2nd or more	10 (28.6%)	855917 (50.4%)	reference

p-value = 0.0157 (Chi-square Test)

Table 5. Prevalence of ABS-L within birthweight compartments

Birthweight compartment (g)	ABS-L (N = 35)	Demographic data (N = 1697438)	Prevalence (N = 0.21)	OR [95% CI]
<2500	11	126134	0.87	5.71 [2.80-11.66]
2500-3999	22	1400449	0.16	reference group
≥4000	2	170855	0.12	

p-value < 0.0001 (Chi-square Test)

Table 6. Sex ratio and prevalence by sex of ABS-L liveborn infants

	ABS-L (N = 35)	Demographic data (N = 1697469)	Prevalence (N = 0.21)
Male	22 (62.9%)	874139 (51.5%)	0.25
Female	13 (37.1%)	823330 (48.5%)	0.16
Sex ratio (M/F)	1.69	1.06	–

p-value = 0.1787 (Chi-square Test)

Table 7. Complications during pregnancy with ABS-L infants

Pregnancy complications	ABS-L (N = 35)	Control group (N = 525)	OR [95% CI]	p-value
Vaginal bleeding and/or spotting	12 (34.3%)	57 (10.9%)	3.70 [1.66-8.27]	0.0014
Upper and/or lower airway infections	8 (22.9%)	38 (7.2%)	3.72 [1.46-9.45]	0.0058
Genitourinary tract infections	4 (11.4%)	60 (11.4%)	1.44 [0.47-4.42]	0.53 (NS)

NS – not significant

significant impact. Werler et al. [19] estimated multivariable-adjusted odds ratios, and reported no significant influence of maternal age, primigravidity, ethnicity, maternal education, and maternal smoking on the prevalence of ABS. According to our findings, young maternal and paternal age, as well as primigravidity, significantly increase the risk of ABS-L when analyzed separately. However, because of close relationship of these variables, we decided to analyze their effect simultaneously, to find out which has the strongest impact on ABS-L prevalence figure. Out of these three, only the young maternal age reached borderline statistical significance (p-value = 0.0508).

It has been postulated that acute febrile maternal illness during the first trimester of gestation, and antipyretic drug (acetaminophen) administration significantly increase the risk of ABS [1, 19]. Since fever is a common indication for acetaminophen use in pregnant women, these two factors are tightly interrelated. Also a higher proportion of vaginal bleeding coexistent with ABS has been reported [1, 2, 27]. In order to analyze in detail the gestational complications, that are often related to maternal age and birth order, we introduced an adjustment for these variables. We found that upper and/or lower respiratory infections and vaginal bleeding and/or spotting convey approximately fourfold increased risk of ABS-L (OR = 3.72; p = 0.0058 and OR = 3.70; p = 0.0014 respectively). The first complication, at least in some instances, might be a possible causative factor of ABS-L, whilst the latter one should rather be considered as a symptom of traumatic amniotic rupture.

Our observations, that ABS-L children were predominantly born with low birth weight, in 36.7 weeks of gestation on average, were consistent with Martinez-Frias et al. [20] and Orioli et al. [1]. We also found preponderance of males (with male to female ratio – M/F = 1.69) which was concordant with Orioli et al. [1] (M/F = 1.17), but opposed to the sex ratio obtained by Martinez-Frias et al. [20] (M/F = 0.86).

From the results of our epidemiological study, we can conclude that young maternal age and respiratory infections complicating normal course of pregnancy may jepordize infants to amniotic damage. However, significance of young age in mothers may be subsidiary, and might not result from itself, but rather from different factors associated with it, such as smoking, alcohol consumption, and recreational drug use [28]. The examination of these factors is difficult, as mothers delivering malformed children, are quite often unlikely to disclose the information on their risky gestational behaviors.

Additional investigations based on bigger samples are needed to confirm our results. Continuous monitoring of the ABS occurrence is an important issue, as it may help to identify more specific factors that underlie pathogenetic processes and lead to the development of this serious congenital condition.

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