CHROMOSOMAL ABNORMALITIES IN COUPLES WITH MALFORMED STILLBIRTHS OR INFANTS

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Abstract: *The paper aims to identify the type and frequency of chromosomal abnormalities in couples with malformed stillbirths or infants deceased, as well as to identify the particularities in such couples. The study was accomplished on 32 couples who had malformed stillbirths or infants deceased. Both members of the couples were investigated through medical and familial anamnesis and conventional cytogenetic analyses. For the identification of couple's characteristics with chromosomal abnormalities, bivariate analysis was realized. In this group of patients, the overall frequency of chromosomal abnormalities was of 4.68%. The balanced chromosomal abnormalities identified were: reciprocal (n=2) and Robertsonian translocations (n=1). Bivariate analyzes revealed the statistical significant differences in male and female age, presence of spontaneous abortion and familial anamnesis positive for reproduction failure in the couples with chromosomal abnormalities.*

Cuvinte cheie: *anomalii cromosomiale echilibrate, translocaţie reciprocă, translocaţie Robertsoniană*

Rezumat: *Lucrarea îşi propune identificarea tipului şi frecvenţei anomaliilor cromosomiale la cuplurile cu nou-născuţi morţi sau feţi plurimalformaţi decedaţi în perioada neo-natală, precum şi identificarea unor particularităţi ale acestor cupluri. Studiul a fost realizat pe 32 de cupluri care au prezentat în antecedente nou-născuţi morţi sau feţi decedaţi neo-natal plurimalformaţi. Cuplurile au fost investigate prin efectuarea anamnezei medicale personale şi familiale şi efectuarea cariotipului constituţional pentru ambii membrii. Pentru a identifica caracteristicile cuplurilor cu anomalii cromosomiale a fost realizată analiza bivariată. Pe acest lot au fost identificate anomalii cromosomiale cu o frecvenţă generală de 4,68%. Anomaliile cromosomiale de structură echilibrate identificate au fost reprezentate de translocaţii reciproce (n=2) şi translocaţii Robertsoniene (n=1). Analiza bivariată a relevat diferenţe semnificative statistic la cuplurile cu anomalii cromosomiale în ceea ce priveşte vârsta medie a consultanzilor, prezenţa avorturilor spontane în antecedente şi anamneza familială pozitivă pentru tulburările funcţiei de reproducere.*

INTRODUCTION

Stillbirths (after 25 weeks of gestational age) are the result of multiple causes, between 5-10% of cases are due to chromosomal abnormalities.(1) Infant's deaths (0-4 weeks after birth) are caused by prenatal factors; chromosomal abnormalities are registered in 2-5% of cases.(1) Some of multiple congenital abnormalities syndromes of stillbirths and infants are caused by the presence of balanced chromosomal abnormalities in one parent. So, the carrier of balanced reciprocal translocation has a risk between 1-20% of having an abnormal child due to segmental aneusomy. The risk is dependent of the translocation type and carrier sex.(1,2) The risk of Robertsonian translocation carrier for having an abnormal child differs according to the type of chromosome involved in translocation (homologous or heterologous translocation) and the carrier's sex.(1,2) In case of pericentric inversion, another balanced chromosomal abnormalities, in one member of the couple, there is a risk between 5-10% according to size and position of inversion, as well as to the chromosome involved.(2)

PURPOSE

Given the role of parental balanced chromosomal abnormalities in malformed stillbirth or infant death etiology, the paper aims at identifying the type and frequency of chromosomal abnormalities involved in this type of reproduction failure, as well as at identifying the particularities of these couples.

METHODS

The observational retrospective study was accomplished on 32 couples. The inclusion criteria were the antecedents of stillbirth or infants in whom the necropsy revealed the presence of multiple congenital abnormalities syndromes. The exclusions criteria were the presence of multiple congenital abnormalities syndromes due to maternal pregnancy exposure to teratogenic agents (biologic, chemical and physical agents) or pathological maternal state (diabetes, maternal phenylketonuria, systemic lupus erythematosus, Graves' disease). In these couples, we realized personal medical history, family inquiries, physical examination and conventional cytogenetic analyses from peripheral blood culture for both members according to the standard protocols.(3) In order to obtain a high level of G banding resolution, cell cycle synchronization with 5-fluorodeoxiuridine and tymidine was realized. The spread banding metaphases without chromosome overlapping were analyzed with an Axioskope 4 Zeiss microscope and karyotyping was realized with Ikaros Meta Systems software. In each case, 30-50 metaphases were analyzed and at least five cells were karyotyped.

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In order to establish the significance between the variables that characterized the couples with chromosomal abnormalities and the couples with normal karyotype, we realized bivariate analyses. The t-test and χ^2test were used for statistical evaluation. The level of significance was $p<0.05$

RESULTS

From the 32 couples, 15 present in their reproductive antecedents, stillbirth malformed child and 17 couples present malformed infants deceased.

The characteristics of couples included in our study were:

- Maternal ages vary between 20 and 38 years old, with a mean age of 28.88 years.
- Paternal ages vary between 23 and 38 years old, with a mean age of 30.38 years.
- Reproductive history revealed the presence of spontaneous abortions in 47% of couples, in which the number varies between 1-5 abortions. Only 20% of couples have spontaneous abortion occurred in the first trimester of pregnancy.
- Family inquires revealed the existence of other cases of reproductive failure in the family for 31% of couples (spontaneous abortion 19%, children with multiple congenital abnormalities syndromes 9%, primary sterility 3%).
- The malformed stillbirths or infants were diagnosed with Down syndrome (25%), Patau syndrome (19%), Edwards syndrome (6%), VACTER malformative association (9%) and other plurimalformative syndromes (41%). Cytogenetic confirmation of syndrome was accomplished in 56% of cases.
- Physical examination of both partners of the couples revealed no particularities. Body mass index (BMI) for female partner varies between 18.37 – 27.89 kg/m^2, with the mean value of about 21.94 kg/m^2, the majority of females (91%) having a normal weight according to BMI (18.50 – 24.99 kg/m^2), 6% are overweight and 3% are underweight. Body mass index (BMI) for the male partner varies between 15.23 – 21.63 kg/m^2, with the mean value of about 18.35 kg/m^2.

Cytogenetic analyses made for both members of the couple revealed the presence of balanced chromosomal abnormalities with the overall incidence of about 4.68%. The prevalence of translocations in females was of 6.24% and in males was of 3.12%, with a female/male ratio of 2:1. These chromosomal abnormalities were represented by 2 reciprocal translocations and 1 Robertsonian translocation (table no. 1).

Table no. 1. Chromosomal abnormalities detected in our group

Chromosomal abnormalities	Females with chromosomal abnormality (n=2)	Males with chromosomal abnormality (n=1)
Autosomes reciprocal translocation	46,XX,t(4;8)(p16;p23)	46,XY,t(11;18)(p15;p11.1)
Robertsonian translocation	45,XX,rob(13q;21q)	-

The translocation t(4;8)(p16;p23) was identified in the female partner of a couple who presents 4 early pregnancy loss and a stillbirth with phenotype suggestive for Wolf-Hirschhorn syndrome, due to adjacent 1translocation segregation (del4/dup 8).

The translocation t(11;18)(p15;p11) was identified in the male partner of a couple who presented two recurrent abortions in first trimester of pregnancy and a female stillbirth with phenotype suggestive for trisomy 18, due to possible translocation segregation of 3:1.

The translocation t(13q;21q) was identified in the female partner of a couple who presented two spontaneous abortions and a female infant with Down syndrome.

Bivariate analyses made on the couples with chromosomal abnormalities and couples with normal karyotype (table no. 2) revealed the presence of statistical significant differences regarding the following variables:

- female's and male partner's ages were younger in the couples with chromosomal abnormalities
- the average number of spontaneous abortions was greater in couples with translocations as against in couples with normal karyotype
- family inquiry revealed the presence of other cases of reproduction failure in family for 100% of couples with translocations and for 24% of couples with normal karyotype.

Table no. 2. Bivariate analyses in couples with and without chromosomal abnormalities

Chromosomal abnormalities in couples with malformed stillbirth or infants			
	No	Yes	P
	N=29	N=3	
Maternal age (years)	29,31±3,86	24,67±0,58	0,049
Paternal age (years)	30,79±3,65	26,33±1,53	0,047
No of spontaneous abortions	0,79±1,29	2,67±1,25	0,022
Maternal weight (kg)	59,17±4,92	55,33±5,83	0,214
Maternal height (m)	1,64±0,05	1,68±0,04	0,119
Maternal BMI (kg/m^2)	22,18±2,26	19,56±1,21	0,06
Paternal height (m)	1,79±0,05	1,81±0,02	0,601
Paternal weight (kg)	86,90±18,6	82±5,29	0,657
Paternal BMI (kg/m^2)	18,49±1,84	16,98±2,13	0,190
Positive family inquiry	24% (29)	100%(3)	0,040
Oral contraceptive	31%(9)	33%(1)	0,560
Existence of healthy child	38%(11)	0	0,496
Pregnancy age (weeks)	35,52±3,43	38±2	0,232

DISCUSSIONS

The literature data notify that maternal fatness in pregnancy is one of the frequent factors involved in the etiology of stillbirth. In our group of patients, we excluded this factor by BMI determination which revealed that majority of our female patients (91%) had a normal value, 6% were overweight and 3% were underweight.

Cytogenetic analyses revealed the presence of balanced chromosomal abnormalities in one member of a couple with an overall frequency of 4.68%, frequency similar to the ones depicted in other studies.(4,5)

The female/male ratio observed in our study is almost similar to the ratio reported in most of the reported studies.(4,5)

The predominance of chromosomal abnormalities in females appears to be due to the fact that chromosomal abnormalities that are compatible with fertility in females may be associated with sterility in males.

The type of chromosomal abnormalities detected in our study is similar to the type reported in other study.(4,5)

The statistical significant differences regarding the ages of couple partners with chromosomal abnormality emphasize the role of chromosomal abnormalities in the production of genetic abnormal gametes in relatively young ages, which give rise to foetus with chromosomal plurimalformative syndromes. According to the segregation of chromosomal abnormalities in embryo, the anomaly is either compatible with survival and gives rise to a malformed child, or is incompatible with life or gives rise to spontaneous abortion.

Family inquiry positive for reproduction failure in the family of couples with chromosomal abnormalities could signify the transmission of derivative chromosome in balanced state, suggesting for the necessity of cytogenetic investigations of the family.

CONCLUSIONS

Parental balanced chromosomal rearrangements are important factors in the etiology of malformed stillbirth or infants.

In the couples with malformed stillbirth or infants, the probability that one member could be the carrier of balanced chromosomal abnormalities is increased by the presence of spontaneous abortions, age of couple's members younger than 30 years old and family inquiry positive for reproductive failure.

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