IDENTICAL MONOCHORIONIC TWINS WITH DOWN SYNDROME AND PATERNAL ORIGIN OF THE EXTRA CHROMOSOME 21

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Abstract: Trisomy 21, the cause of Down syndrome (DS), is the most frequent trisomy in humans. The risk for DS increases with maternal age: mothers under 25 years of age are known to have an average risk of a DS pregnancy of 1:1600, rising to 1:350 at age 35 and to 1:40 at 43, respectively.

Twins with DS are rare. We report on monozygotic (MZ), monochorionic twin sisters with DS, whose parents are young (24 and 26 years old, respectively) and healthy. Family history is non contributory; pregnancy and delivery were uneventful. Both girls presented at birth with clinical manifestations of Down syndrome, that was confirmed cytogenetically (47XX,+21). Microsatellites analysis indicated that the twins are identical and that the extra chromosome 21 was of paternal origin.

Conclusions: For practical purposes, the causative non disjunction should be considered a single sporadic event, with an empirical recurrence risk estimated at about 1%.

Key words: Down syndrome, identical twins, paternal origin.

Introduction

Trisomy 21 occurs in ~1:700 live-born children [1]. Free trisomy 21 is found in ~95% of all cases, mosaicism in ~2 to 4% [2], while in ~5% of cases, one element is translocated to another acrocentric chromosome (most often chromosome 14 or 21) [3–4]. Meiosis errors that lead to trisomy 21 are mostly of maternal origin, while only about 5% occur during spermatogenesis.
We here describe identical, monochorionic twins born to young, healthy parents.

Case report

The monochorionic twins were delivered vaginally after 40 weeks of uneventful pregnancy. A 24-year-old woman and her non-consanguineous 26-year-old husband were of Turkish-Macedonian origin and healthy. There was no family history of spontaneous abortions, early deaths, mental retardation or other birth defects. No prenatal diagnosis was performed. Karyotypes of the parents were normal (46,XX and 46,XY, respectively).

At birth twin A measured between the 25th and 50th centile for length (47 cm) and weight (2410 g) and between the 10th and the 3rd centile for occipito-frontal head circumference (30 cm). Apgar scores after 1, 5 and 10 min were 8, 9 and 10, respectively. Twin B measured between the 25th and 50th centile for length (48 cm), weight (2390 g) and occipito-frontal head circumference (32 cm). Apgar scores after 1, 5 and 10 min were 8, 9 and 10, respectively.

As the features of both twins (flat face, upward and slanted palpebral fissures and epicantic folds) were suggestive of Down syndrome (DS), chromosome analysis from peripheral lymphocytes was performed. The karyotype was 47,XX,+21 in both cases and in all metaphases (n = 20) investigated by conventional Giemsa-banding (500 bands). Clinical and ultrasound examination showed no renal or cardiac malformations. Thyroxine and TSH levels were normal. At the age of 7 months no hypotonia or significantly delayed motor functions (control of head and sitting position) were noticeable. The facial features were those typical of DS.

DNA was extracted from peripheral lymphocytes of both twins and their parents using standard protocols. Genotyping by microsatellite analysis was performed on the family with the following markers from chromosome 21: D21S1904, D21S1911, D21S1919, D21S1899, D21S1922, D21S1884, D21S1255. Fluorescently labelled primers were amplified by standard conditions and PCR products were run and analyzed on a 3130 Genetic Analyzer (Applied Biosystems).

Segregation analysis of microsatellite markers showed that both sisters had identical genotypes at all the analysed loci. A two-alleles pattern was observed for each marker with a peak of double height for the allele of paternal origin. This pattern suggests that trisomy 21 arised from non disjunction at paternal meiosis II.
Discussion

Twins with DS are a rare [5–12]. Only 1.2% of twin pregnancies result in one twin having DS. Even rarer are the pregnancies which end with the delivery of both twins having DS. In only 1/6 of the twins both children have Trisomy 21 [13]. Interestingly, the no DS was found in twin pregnancies, but 0.9% DS were found in singleton pregnancies (0.9%) [14]. The specificity of our twins is that they are both monozygotic and monochorionic.

Grynberg et al. (2007; 11) reported on bichorionic, biamniotic, monozygotic twin fetuses with trisomy 21 and different phenotypes: twin A had increased nuchal translucency, while twin B had a cervical cystic hygroma and heart defect. An anorectal malformation was described in another pair of DS monozygotic twins [15]. In a pair of dizygotic twin boys born after ICSI, one twin had trisomy 21, while the other had a complex heart defect and oesophageal atresia, but no DS [7].

A 46,XY/47,XY,+21 mosaicism has been reported in twins with DS [10]. In another case of dizygotic twins one had trisomy 18 and the other trisomy 21 [16], and yet in another case one twin had trisomy 21 and the other had monosomy X [17]. A possible coincidence of double aneuploidy (Klinefelter, DS) in newborn twins was also observed [18].

Parental origin and mechanisms of formation of aneuploidy can be studied using DNA polymorphic markers. Only 6–7% of DS cases originate from paternal meiotic errors, mostly at meiosis II [1]. The vast majority of meiotic errors are of maternal origin [22]. In 5% of trisomic individuals the supernumerary chromosome 21 appears to result from a mitotic error, usually giving rise to mosaicism. In the present case, which resulted from a spontaneous pregnancy, analysis of 7 microsatellite markers from chromosome 21 showed that both twins had the same extra chromosome 21 of paternal origin, originating from non disjunction at meiosis II. These findings are of practical relevance, allowing to conclude for a sporadic event, with an empirical recurrence risk of about 1%.

In summary, our monozygotic, monochorionic twins are remarkable for the paternal origin of the extrachromosome 21, and for the young age of parents. The case appears to be worth reporting, given that knowledge of parental origin and mechanisms of formation of chromosomal aberrations in twins is still scarce.

REFERENCES


Резиме

ИДЕНТИЧНИ МОНОХОРИОНСКИ БЛИЗНАЦИ
СО ДАУНОВ СИНДРОМ И РОДИТЕЛСКО ПОТЕКЛО
НА ЕКСТРАХРОМОЗОМОТ 21

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Апстракт: Трисомијата 21, или Дауновиот синдром (ДС) е најчеста трисомија кај луѓето. Ризикот за појава на ДС се згодемува со згодемување на возраста на мајката, мајки под 25 години имаат ризик од 1 : 1600, на возраст од 35 години 1 : 350, а на возраст до 43 години 1 : 40.

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Близнаци со ДС се ретки. Ни прикажуваме моноzigотни, монохорионски сестри близначки од млади и здрави родители (24 и 26 години). Фамилината анамнеза е нормална, како и бременоста и породувањето. Двете сестри имаа јасен ДС фенотип кој беше потврден со цитогенетска анализа (47XX,+21). Микросателитната анализа покажа дека екстра хромозомот е со патернално потекло.

Заклучок: за практични причини козативната не-дисјункција треба да се смета за единствен спорадичен настан, со емпириски ризик за рацидив од околу 1%.

Ключни зборови: Даунов синдروم, идентични близнаци, патернално потекло.

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