Cytogenetic Study in Children with Down Syndrome Among Kosova Albanian Population Between 2000 and 2010

Selim Kolgeci1, Jehona Kolgeci2, Mehmedali Azemi3, Ruke Shala-Beqiraj4, Zafer Gashi5, Mentor Sopjani2
Obstetrics and Gynecology Clinic, University Clinical Center of Kosova, Prishtina, Kosova1
Faculty of Medicine, University of Prishtina, Prishtina, Kosova2
Pediatric Clinic, University Clinical Center of Kosova, Prishtina, Kosova3,
Department of Histology and Embriology, University Clinical Center of Kosova, Prishtina, Kosova4
Policlinic “Biolab-Zafi” IVF (center), Klina, Kosova5

Corresponding author: Assoc prof Selim Kolgeci, Obstetrics and Gynecology Clinic, University Clinical Center of Kosovo, Muharrem Fejza street nn, Prishtinë, tel: +377(44) 208-017; E-mail: selimab@hotmail.com

ABSTRACT

Aim: The aim of this research was to ascertain the frequency of three basic cytogenetical types of Down syndrome among Kosova Albanian population and to evaluate the maternal age effect on the frequency of births of children with Down syndrome. Methods: Cytogenetics diagnosis has been made according to the standard method of Moorhead and Seabright. Results: In the time period 2000-2010 cytogenetics diagnosis of overall 305 children with Down syndrome has been realized. Of which in 285 children (93.4%) were found free trisomy 21 (regular type), and in three other children (~1.0%) were detected mosaic trisomy 21. Translocation trisomy 21 was detected in 17 children (5.6%), of which in 14 children it occurred de novo translocation, whereas in 3 other children translocation has been inherited by a parent translocation carrier. The highest number of children with Trisomy 21 due to translocation was caused by Robertsonian translocation created by a fusion of two homologous chromosomes 21 (3.3%). Analysis showed that the number of children born with Down’s syndrome, from 2000 to 2010, was not decreasing among the Kosova Albanian population. Conclusion: Down syndrome resulted by an extra free chromosome 21 is the most common genetic cause for that condition. Robertsonian translocations present in Down syndrome children often are de novo or inherited from a carrier parent with translocation. Key words: Down syndrome, free trisomy 21, Robertsonian translocation.

1. INTRODUCTION

Down syndrome is the most common chromosomal disorder in humans. Its prevalence in Europe is about 9.8:10 000 live born infants (1), while in the USA it is 8.5:10 000 newborns to mothers younger than 35 years of age and up to 55.3:10 000 newborns among mothers older than 35 years of age (2). Genetic cause for this syndrome is trisomy of chromosome 21 or the presence of distal part of the long arm of chromosome 21. In Down syndrome patients there are present three types of cytogenetic trisomy 21, i.e.: free trisomy 21, mosaic trisomy 21, and translocation trisomy 21 (3).

Most commonly, Down syndrome children have karyotype of free Trisomy 21, while their parents have normal karyotype. This type of trisomy 21 exclusively occurs sporadically de novo as a result of nondisjunction of homologous chromosomes 21 during gametogenesis to parents or during early embryonic development after fertilization (4). Analysis of chromosome heteromorphisms and many other informative markers of DNA polymorphisms of parents and their offspring with Down syndrome revealed that chromosome 21 nondisjunction occur more often during the gamete-formation process in females than in males (5, 6). Investigations found that an extra chromosome 21 mainly originates from errors in maternal side in approximately 90% of the Down syndrome cases.

In 5-10% of Down syndrome cases the extra chromosome 21 originates due to errors in father side, whereas in less than 5% of cases it results from nondisjunction of chromosomes during a post-zygotic mitosis in early embryonic development (7, 8). Important role for chromosome 21 nondisjunction has also maternal age. Older woman is more likely to have a chromosome 21 nondisjunction during cogenesis than young women (9), Therefore older women have a higher risk of having a baby with Down syndrome.

In children with Down syndrome due to translocation trisomy 21, extra chromosome 21 is joined or translocated in any other acrocentric or non-acrocentric chromosome (10). The translocation trisomy 21 present in Down syndrome patients can be created spontaneously de novo during gametogenesis in one of the parents or it can be inherited from parents’ carrier of Robertsonian translocation or of reciprocal translocations. Studies indicated that in the case of children having Trisomy
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21 with Robertsonian translocation created sporadically de novo, the risk for a second future offspring trisomy 21 for their parents with normal karyotype is small. There is a significant increased risk of giving birth to a child with Trisomy 21 when one parent is a Robertsonian translocation carrier or of reciprocal translocations as they may produce balanced and unbalanced gametes during gametogenesis (11, 12). When one parent is carrier of Robertsonian translocation 21q: 21q, it has 100% chance of having a Down syndrome child as all of its produced gametes are unbalanced (13). The frequency to have one child with Down’s syndrome due to translocation trisomy 21 is not influenced by the age of the mother.

Peoples with mosaic Down syndrome have two distinct cell lines with different karyotype. In some cells there are a total of 46 chromosomes having normal karyotype, while other cell lines have karyotype with Trisomy in chromosome 21 (14).

Many authors argued that restricting or reducing the births for woman’s who are aged 35 years or older, mandatory prenatal cytogenetics diagnosis of fetal disorders of pregnant women aged 35 years or older, and applying the methods for prenatal screening on all ages pregnant women’s reduce the number of births of children with Down syndrome (15,16).

We realized our study on the rate of birth of children with Down syndrome in Kosova Albanian population for the time period 2000-2010, when Kosova have had no conditions for full application of methods as described above in order to prevent birth of children with Down syndrome in our population.

2. AIM
The purpose of this study was to found the frequency of the 3 cytogenetic types of Down syndrome among Albanian population of Kosova, as well as to evaluate the maternal age effect on the prevalence of Down syndrome births.

3. METHODS
Cytogenetics analysis has been realized on chromosome preparations of lymphocytes cultured from peripheral blood according to Moorhead method (17). For precise identification of chromosomes standard method for G-banding by Seabright was used (18). Cytogenetics diagnosis of all investigated cases has been carried out in the cytogenetics laboratory of the obstetric and gynecology clinic in Prishtina. Since that lab is the only laboratory for cytogenetics in Kosova, all baby suspected of having Down syndrome were diagnosed there, thus that laboratory has most accurate information regarding to the Down syndrome cases among Kosova’s population.

4. RESULTS
During a 10 years period, 2000-2010, in the Obstetrics and Gynecology Clinic in Prishtina there have been found 305 children with Down syndrome cytogenetically diagnosed. Out of that 193 (63.3%) were males, while 112 (36.7%) females. The sex ratio has indicated the prevalence of the males for the total sample 1.72:1 (193:112) as well as for the three basic cytogenetic types of Down syndrome (Table 1). In all of the Down syndrome diagnosed cases, free trisomy 21 was present in 285 (93.4% of cases) patients, with cytogenetic formula 47,XX,+21 or 47,XY,+21 (Table 2). Mosaic Down syndrome was found in three cases (1.0%). All the parents of children having free trisomy 21 and mosaic Down syndrome have had normal karyotype. Down syndrome due to translocation trisomy 21 was detected in 17 (5.6%) children (Table 2). Cytogenetical analysis of the parents of children affected with translocation trisomy 21 revealed that in three children (1.0%) translocation was inherited by one of carrier parent of that translocation, from the mother respectively. The other 14 (4.6%) children with this Down syndrome type have had de novo translocation.

One child with Down syndrome had inherited his translocation 8;21 from the mother. He was a carrier of reciprocal translocation 8;21 and of trisomy 21, with cytogenetic formula: 47,XY,t(8;21)(q22;q22)mat,+21. The child’s mother was a silent carrier of a balanced translocation with karyotype: 46,XX,t(8;21)(q22;q22). The child having this chromosomal aneuploidy was as a result of disjunction 3:1 of derived chromosomes 8 and 21 and their normal homologues during gametogenesis in his mother (Interchange trisomy 21).

Second child with Down syndrome inherited translocation from the mother who was a Robertsonian translocation silent carrier with translocation involving 14q;21q, with karyotype: 45,XX,der(14;21)(q10;q10). Karyotype of the child was 46,XX,der(14;21)(q10;q10)mat,+21 as a result of disjunction 2:1 and of adjacent-1 segregation during meiosis in her mother.

Third child with Down syndrome inherited translocation...
also from the mother silent carrier of Robertsonian translocation 21q:21q, with karyotype 45,XX, der(21;21)(q10;q10). The child has a karyotype 46, XY,+21,der (21;21)(q10;q10) mat caused by joining of disomic gamete for chromosome 21 of the silent translocation carrier mother with normal gamete of partner.

In 16 children (5.2%) there have been detected trisomy 21 with Robertsonian translocation created by merging of chromosome 21 with another acrocentric chromosome. Most of investigated children had Robertsonian translocation formed between two homologous chromosomes 21. This translocation type is found in 10 (3.3%) investigated children (Table 3). In 4 (1.3%) other children had trisomy 21 with Robertsonian translocation between chromosomes 21 and 14. Robertsonian translocations between chromosome 21 and 13; and between 21 and 15 were present only in one child (0.3%) each. Reciprocal translocation between chromosome 21 and 8 was found only in one child (0.3%) with Down syndrome.

In this study is presented the birth frequency of children of Down syndrome is lower due to the smaller number of women births compared to higher risk among older women, therefore Down’s syndrome children born to mothers of advanced age 21-30 years gradually increasing. This increase is in correlation with the increasement of total number of births in the general population as well, which occurs most frequently at those ages in parallel with the birth of children with Down syndrome. Although the number of children born with Down syndrome in this period at first sight seems to be higher, however if the number is analyzed for total ratio of births at this period it shows no higher incidence than in older women. There is a small decrease in the frequency of live births with Down syndrome among women aged 30-35 years. This decrease can be related to the reduction in the total number of births in general population, where the birthrate of women over the age of 35 gradually decreases until the end of their reproductive periods. In the general population, there is a parallelism on increasing the number of births of normal and of Down syndrome children by age of 35. Women aged 35 to 40 have a permanent increase of the birth of children with Down syndrome which is not in proportion with the increase of births in the general population, since at this age the number of births in the general population decreases. The increase of Down syndrome births to mothers in this age showing a direct correlation between Down syndrome and maternal age, thus the linkage of advanced maternal age to...
an increased risk of Down syndrome births.

Figure 3 shows Down syndrome live births occurred among mothers aged between 15-35 years and of those 36-55 years of age in 2000-2010 time period. It should be noted that in the year 2000 (first year after the war in Kosovo) the number of Down syndrome births were two times more likely to occur to mother younger than 35 compared to those of 36 years of age or older. Most of mothers of these children have started their pregnancy in 1999, at the end of the war in Kosovo; however, there is no detail information about their war trauma experience, in order to correlate to the possible impact of trauma on non-disjunction of chromosome 21 during gametogenesis to young mothers.

5. DISCUSSION

Cytogenetics studies performed on 305 Down syndrome cases revealed that translocation trisomy 21 was found in 17 cases (5.6%) (Table 2). Our results are roughly similar to the results of other authors (3, 15, 19). Most children with translocation Down syndrome are born to mothers under the age of 35; therefore not depend on maternal age. Chromosome 21 most frequently creates translocations with acrocentric chromosomes than to other non-acrocentric autosomal or sex chromosomes. Our findings conclusively argue that as well, where Robertsonian translocation between chromosome 21 and another acrocentric chromosome have been found in 16 children, while in only one child there was present reciprocal translocation between chromosomes 8 and 21.

The findings of some other authors (20) reported high presence of Robertsonian translocation 14q: 21q in children with translocation trisomy 21 (62.34%). In our study the most frequent type of translocation were the Robertsonian translocation 21q: 21q (58.8%) (Table 4). The second most frequent (23.5%) translocation type was the Robertsonian translocation 14q: 21q. Other Robertsonian translocation types were less present in our study cases. There has been reported that in 75% of all translocation cases it may occur de novo, while in 25% of cases, it can be inherited from one carrier parent, but more frequently by the mother side (21). In our present study spontaneously de novo translocation occurred in 82.4% of children, while in 17.6% of children inherited from a carrier parent, mothers respectively.

To prevent the birth of children with Down syndrome in translocation affected families the early detection of parent's carriers with Robertsonian translocation involving chromosome 21 is of the great importance. In the families who have children with translocation trisomy 21 arisen de novo i.e. when the parents have normal karyotype, the risk of giving birth to a child with translocation trisomy 21 is small (1-2%). Therefore, parents of 14 children with translocation trisomy 21 occurred as de novo event studied in our paper do not have high risk of giving birth to a second child with trisomy 21. Since an affected child with reciprocal translocation 8:21 and an another child with Robertsonian translocation 14q: 21q, have inherited translocation from their mother side, the recurrence risk is significantly much higher (10-15 %). By applying the prenatal cytogenetic diagnosis of embryos of each of these couple pregnancies can be prevented the spread of Down syndrome within a generation. To our knowledge, all published papers for couples which are carriers of silent Robertsonian translocation involving homologous chromosomes 21q: 21q have reported 100% risk of having a child with Down syndrome and unable to have healthy baby (13, 22). In our study a Down syndrome child inherited Robertsonian translocation 21q: 21q from a carrier mother. This family is unable to have healthy child by embryo selection through prenatal cytogenetic diagnosis due to the fact that carrier mother can only make unbalanced gametes, thus any of her child will have Down's syndrome.

The cytotgenetical study conducted on 305 Down syndrome children among Albanian population of Kosovo revealed that free trisomy 21 is significantly more frequent (93.4%) than the other types of trisomy 21. Other authors also indicated high occurrence of free trisomy 21 (92-95%) in children that have Down syndrome (3, 15, 19). It shows that this chromosomal aberration is presented equally as frequent as in rest of the world. Since the free trisomy 21 is the most common genetic cause of birth of children with Down syndrome it is of great importance to undertake preventive measures in order to reduce the disorder incidence among human population. For prevention purposes, the etiological factors as a cause of birth of children with Down syndrome, should be known, and reduction measures should be taken to minimize impact.

Studies of many authors have shown that one of the factors which increase the incidence of births with free trisomy 21 is advanced maternal ages (15, 23, 24). Very often Down's syndrome babies are born to mothers who are over 35 years of age. The results of our paper have also confirmed that a woman over 35 years of age to have highest incidence of giving birth to a child with Down syndrome. (Figure 2).

A relatively simple way to reduce birth incidence of Down's syndrome is the limitation or reduction of the number of pregnant women older than 35 years. The frequency of birth of children with Down syndrome is expected to be reduced up to 20-45% with the birth limiting to mothers aged over 35 years (15). Prenatal preventive diagnostic tests for Down syndrome in modern medicine can be realized through the application of either non-invasive tests (ultrasound and biochemical screening) or by invasive diagnosis methods such as chorionic villus sampling, amniocentesis, cordocentesis. Antenatal careening using different biochemical markers and ultrasound are made routine in developed countries, where their national prenatal care policies obliges amniocentesis to all pregnant women aged 35 years or over, as well as maternal serum screening for younger women. To prevent the birth of child with Down syndrome recently there are considered some other preventive strategies, such as: pre-implantation genetic diagnosis (PGD) and folic acid supplementation (25). As in Kosovo currently there are no conditions for application of the above mentioned methods to prevent the birth of child with Down syndrome, during our cytogenetics study in children there was not observed a gradual decrease in the frequency of birth of Down syndrome among Albanian population of Kosovo in 2000-2010 (Figure 1).

6. CONCLUSIONS

Based on the results of present study the following conclusions can be drawn:

- Free Trisomy 21 has been found in 93.4% of children with Down syndrome.
- Translocation ttrisomy 21 was present in 5.6% of children with Down syndrome.
- Most of the children with Robertsonian translocation had...
translocation formed by the homologous chromosomes 21 (3.3% of cases).
- Mosaic trisomy 21 was present in 1.0% of Down syndrome children.
- Down syndrome among Kosovo Albanian population was more frequent in males (63.3%) than females (36.7%).
- Children with free trisomy of chromosome 21 are more frequently born to mothers older than 35 years of age.
- Advanced maternal age appears not to affect the frequency of giving birth to a child with translocation trisomy 21.

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