Cytogenetic and epidemiological profiles of Down syndrome in a Moroccan population: a report of 852 cases

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ABSTRACT

Introduction: Trisomy 21 or Down syndrome is the most common type of autosomal chromosome abnormality, with an incidence of one out of 700 live births. Down syndrome is associated with psychomotor delay, characteristic facial features, and sometimes, cardiac, digestive and ocular malformations. The aim of this study was to estimate the proportions of various cytogenetic types of trisomy 21, and to study the link between maternal age and trisomy 21 in the Moroccan population, in order to provide data on the cytogeneticity and epidemiology of Down syndrome in Morocco.

Methods: A retrospective analysis was performed on the case records of 852 patients who were confirmed as Down syndrome by cytogenetic analysis at the Department of Medical Genetics, National Institute of Health, Morocco.

Results: Among the 852 cases of Down syndrome presenting over a period of 15 years, free trisomy 21 was present in 820 cases (96.24 percent). 27 patients had translocation and five cases were mosaics. The median maternal age of the Moroccan mothers at the birth of the affected child was 35.39 years.

Conclusion: The identification of specific types of chromosomal abnormalities in Down syndrome children is important as it assists with patient management and family counselling.

Keywords: cytogenetic analysis, Down syndrome, karyotype pattern

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INTRODUCTION

Down syndrome is the most common type of chromosomal trisomy found in newborns, with an incidence of one out of 700.[1] Down syndrome is associated with mental retardation and characteristic facial features. A clinical diagnosis of Down syndrome may be unconfirmed in one third of cases.[2] Down syndrome results from the presence of an extra chromosome 21, either "free", as a part of Robertsonian fusion, or in rare instances, as a part of reciprocal translocation.[3] In 95% of cases, Down syndrome results from non-disjunction, with the error being predominantly in meiosis I.[4]

The cause of the non-disjunction error is not known, but there is a definite connection with maternal age. Advanced maternal age remains the only well-documented risk factor for maternal meiotic non-disjunction. The incidence of trisomy 21 conceptions increases with maternal age.[1] There is a high incidence of spontaneous foetal loss during pregnancy. Between 11 weeks of gestation and term, 43% of affected pregnancies are spontaneously lost.[5]

The present study aimed to evaluate the karyotype pattern in children with Down syndrome and to study

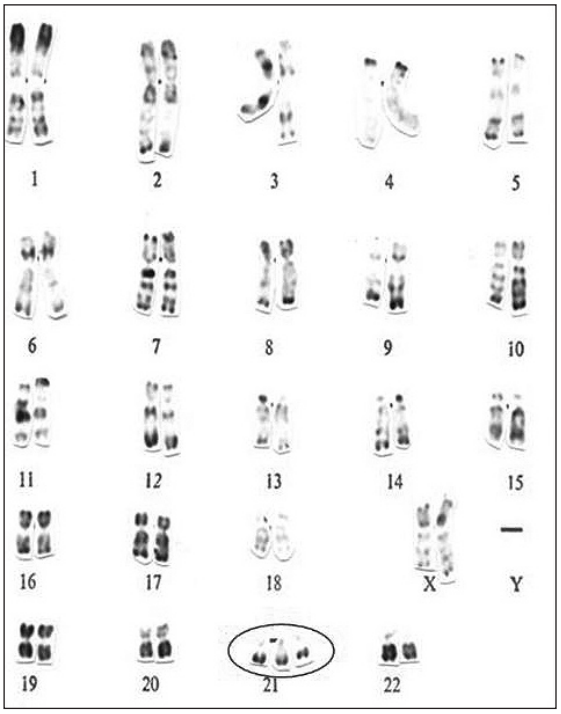

Fig. 1 Original karyotype showing a free trisomy 21. The three chromosomes 21 are surrounded.

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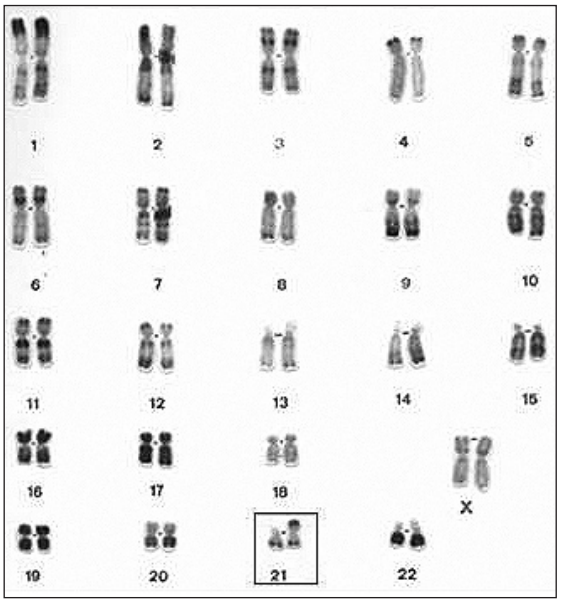

Fig. 2 Original karyotype showing trisomy 21 by translocation *t*(21;21). The three chromosomes 21 are surrounded.

the link between maternal age and trisomy 21 in the Moroccan population.

METHODS

The Department of Medical Genetics at the National Institute of Health, Morocco, is a referral laboratory for cytogenetic investigation. The study included 852 children (486 males and 366 females) ranging from newborns to 15 years of age. Specifically, there were 138 newborns, 457 infants and 257 children. They were referred to the department between 1993 and 2007 for cytogenetic analysis in order to confirm the clinical diagnosis of Down syndrome. Among these trisomic children, three had been born following medically assisted procreation. All the cases in this study were sporadic, except for two couples who had two children with trisomy 21. The parents of children with trisomy 21 by translocation were convened later for chromosomal analysis. There was also a sample of 400 normal newborns, which made it possible to estimate the maternal age at birth of non-trisomic children.

Chromosome preparation was carried out from peripheral blood collected in sodium heparine in all the subjects, and cultures were harvested using standard cytogenetic procedures. Banding techniques were used to classify the chromosomes: the reverse banding technique (RHG banding) or G-banding technique using Trypsin (GTG banding). RHG or GTG-banded chromosomes were karyotyped according to the International System for Human Cytogenetic Nomenclature (ISCN 2005),[6] and the abnormalities were detected. The parents of children who had trisomy 21 by translocation were investigated to confirm the character of the anomaly.

Table I. Different karyotypes showing trisomy 21 by translocation.

Child	Father	Mother
46,XX,der(13;21),+21	46,XY	45,XX,der(13;21)
46,XY,der(14;21),+21	45,XY,der(14;21)	46,XX
46,XX,der(14;21),+21	46,XY	46,XX
46,XX,der(21;21),+21	46,XY	46,XX
46,XY,der(21;21),+21	46,XY	46,XX
46,XY,der(14;21),+21	46,XY	45,XX,der(14;21)
46,XX,der(13;21),+21	46,XY	46,XX
46,XY,der(22;21),+21	46,XY	46,XX
46,XY,-13,der(13;21),+21	46,XY	46,XX
46,XY,der(14;21),+21	46,XY	46,XX

RESULTS

Among the 852 cases, 820 (96.24%) were found to have free trisomy 21 (Fig. 1), five had mosaic trisomy 21 and 27 had translocation (Fig. 2). In the 27 cases with Robertsonian translocation, the chromosome 21 was associated with another acrocentric chromosome of Group D (chromosomes 13 and 14) or Group G (three *t*[21;21]). The hereditary character of the translocation was found in six out of all the cases with translocation. In five cases, the mother was the carrier of the balanced translocation: *t*(13;21) or *t*(14;21). In the sixth case, the father was the carrier of a balanced translocation *t*(14;21). The karyotypes with translocation are listed in Table I.

The median maternal age of the Moroccan mothers of children with trisomy 21 was 35.39 years old. This was significantly higher than the maternal age of mothers of non-trisomic children, whose age did not exceed 27.7 years (Fig. 3). The family investigation also enabled us to determine the row of birth of each trisomic child among the brothers and sisters (Fig. 4).

DISCUSSION

Trisomy 21 or Down syndrome is a common birth defect, and is the most frequent and most recognisable form of mental retardation. Clinical diagnosis of this condition is usually done without difficulty. The diagnosis of Down syndrome, on the basis of clinical features in the neonatal period, has been reported to range from 73% to 100%.[7,8]

The distribution of different anomalies associated with Down syndrome in the present study is very similar to that found in earlier reports. Among 852 children with Down syndrome, free trisomy 21 was found in 96.24% of cases, similar to other studies, in which the incidence

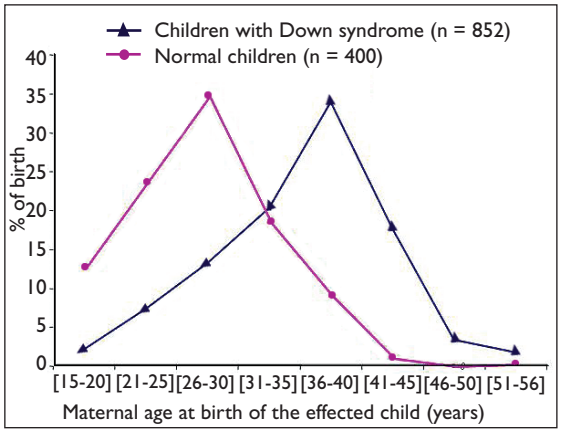

Fig. 3 Prevalence of normal and trisomic newborns according to maternal age at term (current study).

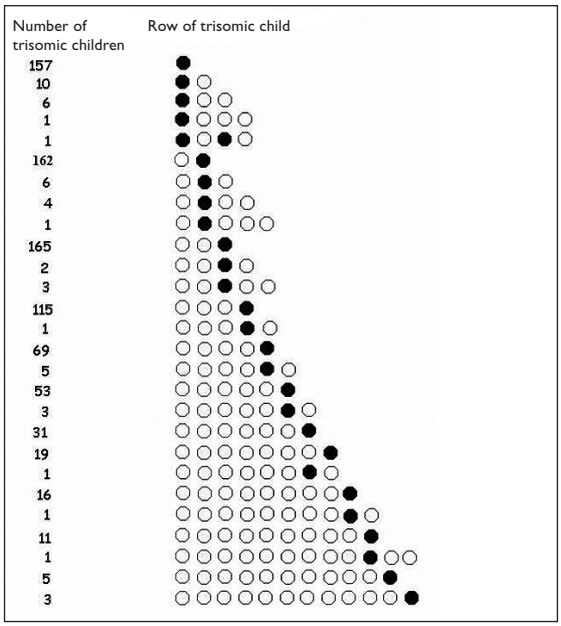

Fig. 4 Row of birth of trisomic child (n = 852).

ranged from 84.6% to 95%.[9-11] This study found 27 (3.17%) cases with Robertsonian translocation. The value of this frequency is similar to a study performed in the Sultanate of Oman but lower than that found in other studies.[12-15] Only 0.59% of patients with Down syndrome in the present study were mosaic. A few previous international studies have reported that the frequency of Down syndrome mosaicism varies from 0%–4.6%.[16,17] Most mosaic cases result from a trisomic zygote with mitotic loss of chromosome 21 after fecundation.

The mechanism of free trisomy 21 is the non-disjunction of the two chromosomes 21 during the meiosis. Advanced maternal age remains the only risk factor for trisomy 21.[18] The risk of having a child with Down syndrome increases as a woman gets older (Table II).[19] Several factors have been incriminated, but they would not modify this risk. These include paternal age, nicotinism, infections, irradiations and hormonal therapy. The median maternal age of Moroccan mothers of children with trisomy 21 was 35.39 years. This is significantly higher than the maternal age of mothers of non-trisomic children (27.7 years). A second child with free trisomy 21 in the same family was rarely reported in our study (there were only two cases of this), and its incidence is exceptional in the literature.

Table II. Frequency of trisomy 21 at delivery according to maternal age.[19]

Maternal age	Risk of trisomy 21
20 years	1/1480
25 years	1/1350
30 years	1/940
35 years	1/353
40 years	1/85
45 years	1/30

The aim of antenatal diagnosis is to propose the best quality of life by having healthy children. In this study, 40% of trisomic patients were born after at least four healthy births. Therefore, the incidence of mental retardation due to trisomy 21 can be reduced by 40% if birth-control was practised in these cases. Genetic counselling is an important process to explain the disease, its causes, complications and treatment. It also allows the parents to understand the recurrence risk and the possibilities of prenatal diagnosis.

In free trisomy 21 homogeneous or mosaic, the karyotypes of the parents are not required. The geneticist will reassure the couple that the risk of recurrence is the same as that of the general population and that it depends on the age of the mother. The second mechanism is trisomy 21 by Robertsonian translocation. It is an accident in half of the cases; the karyotype of the parents is obligatory and confirms the character of the anomaly. Genetic counselling is similar to the one conducted in free trisomy 21. In the case of familial Robertsonian translocation with Down syndrome, the genetic risk of the female carrier having a live born child with translocation in Down syndrome is about 20% if the mother is a carrier, and 5% if the father is a carrier.[20] The geneticist will inform the couple of the possibilities of antenatal diagnosis, if desired. In rare cases, trisomy 21 by translocation involves two chromosomes 21. If one of the parents is carrying this translocation in a balanced state, the risk of recurrence is 100%.

Thus, in Down syndrome, free trisomy 21, Robertsonian translocations and mosaicism are the

classical anomalies. It is important to consider non-classical Down syndrome cases in genetic counselling and to provide precise information about the recurrence risk for such distinct groups. These different cytogenetic patterns in our study are similar to those reported in other surveys.

In conclusion, free trisomy 21 was found in 96.24% of the subjects in this study. Karyotyping is essential for the confirmation of the clinical diagnosis and the determination of the recurrence risk, as well as to provide a basis for genetic counselling. A karyotype of the parents is required only if trisomy 21 is due to a translocation. Advanced maternal age is the principal risk factor for trisomy 21. This risk must be taken into account by couple candidates for medically-assisted procreation. Consultation with the geneticist is essential for these couples.

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