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Cytogenetic Profile of Individuals with Mental Retardation

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KEY WORDS Mental retardation; cytogenetics; microcephaly; trisomy 21

ABSTRACT The incomplete development of mental capacities and associated behavioural abnormalities are referred to as mental retardation. It is single largest neuropsychiatric disorder in every civilised society affecting 2.5-3.0% of the total population. Chromosomal abnormalities are the important cause of mental retardation. Cytogenetic investigations were carried out on 143 mentally subnormal individuals that were referred to the Centre for Genetic Disorders, Guru Nanak Dev University, Amritsar, India, during 1996 to 2002. These cases were referred mainly as suspected Down syndrome, delayed milestones, mental retardation, etc. The age group of the patients ranged from 1 month to 18 years. Interestingly, maximum number of patients i.e., 58/143 (40.5%) were the firstborns and the average maternal age was 27.6 years. Free trisomy 21 was found to be the most frequent autosomal aberration, both amongst males and females (45.4% males, 18.8% females). It was seen in 92/143 (64.3%) cases while translocations were seen in 2.7% cases. The latter included 45,XY,+t(13;14), 46,XY,+t(14;21), 45,XX,+t (14;21) and 46,XX,+t(14;21) karyotypes.

INTRODUCTION

Mental retardation (MR) is due to a variety of genetic and environmental factors. It is manifestation of brain dysfunction that originates during the developmental period, resulting in the limitation of two or more adaptive skills i.e., communication, self care, home living, social skills, self direction, health, safety, leisure, work etc. In India, the incidence of mental retardation is reported to be 2-3%. Of these, 30% cases of severe mental retardation are genetically determined. Out of these, 25% fall under the category of X-linked mental retardation (XLMR) disease, comprising over 100 varied types of retardations that can be associated with fragile-X chromosome, biochemical defects, neurological aberrations, bony dysplasia and a range of other disorders (Gracia 1998). Monosomies and trisomies are reportedly the frequent cause of mental retardation. The early diagnosis of MR is essential for child's health care, medical treatment, facilitation for evaluation of prognosis and for the estimation of risk of recurrence.

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SUBJECTS AND METHODS

Chromosomal investigations were undertaken on 143 patients with mental retardation that were referred to the Centre for Genetic Disorders, Guru Nanak Dev University, Amritsar, during the years 1996-2002. These cases were referred from different districts of Punjab and had been referred for cytogenetic evaluation as the cases of suspected Down syndrome, mental retardation, delayed milestones, congenital anomalies, mental retardation with bone deformities, hyperkinetic child with mental retardation, etc. The cases referred for diagnosis were in the age group ranging from 1 month to 18 years. Among these 44 (30.7%) were females and 99 (69.2%) were males.

Chromosomal preparations were made from peripheral lymphocytes using standard culture technique with modifications. RPMI 1640 medium and phytohemagglutinin stimulated blood lymphocytes were used to set up cultures and chromosomal banding was done by Trypsin-Giemsa (GTG) method (Kaur et al. 1996). In each case 50 to 100 metaphases were examined for numerical as well as structural abnormalities and at least 5 metaphases were karyotyped with Quips (Vysis) Automatic Chromosomal Analysis Programe. Apart from lymphocyte culturing, detailed pedigree analysis and in-depth evaluation of clinical reports was undertaken. Cytogenetic studies were carried out after obtaining parental or patient's consent.

RESULTS AND DISCUSSION

Chromosomal abnormalities in 143 cases were investigated. Out of these 97 (67.8%) showed

abnormal karyotype, of which 68 (47.5%) were males and 29 (20.2%) females. The maximum cases i.e., 65 (45.4%) males showed 47,XY,+21 karyotype and 27 (18.8%) females showed 47,XX,+21 karyotype. A family having two siblings with Robertsonian translocation showed the karyotype 46,XY,+t(14;21) and 46,XX,+t(14;21) respectively. Cytogenetic analysis of their mother revealed the translocation 45,XX,+t(14;21). In another case, a phenotypically normal male showed 45,XY, + t(13;14) chromosomal complement. Modi et al. (1998) in a study of malformations and Down syndromes (DS) in Baroda region reported an overall prevalence of 1.04% per 1000 births, and increased maternal age specific prevalence of DS from 0.54/1000 at age 15-19 years to 15.6/1000 at age >40 years. Verma et al. (1998) reported that in Delhi region the frequency of Down syndrome was 0.81/1000 and 13 DS babies karyotyped by them showed free trisomy. Trisomy 21 was observed as the cause of Down syndrome in majority of the cases in our study also. The average maternal age in 110 DS cases was 27.6 years in our study whereas Seema et al. (2002) has reported it to be 26 years in a similar report from Mumbai. In the present study, the maximum DS children (44) were the firstborns (Table 6).

Table 1: Cytogenetic analysis of male patients referred with Down syndrome (n=75)

No. of cases	*Phenotype*	*Karyotype*
65	Abnormal	47,XY,+21
1	Abnormal	46,XY,+t(14;21)
9	Abnormal	46,XY

Table 2: Cytogenetic analysis of female patients referred with Down syndrome (n=35)

No. of females	*Phenotype*	*Karyotype*
27	Abnormal	47,XX,+21
1	Abnormal	46,XX,+t(14;21)
1	Normal	45,XX,+t(14;21)
6	Abnormal	46,XX

Table 3: Average age of parents at the time of birth of the proband

	Down syndrome cases (Mean±s.d.)	*Mental retardation and related disorders (Mean±s.d.)*
Average maternal age	27.6±5.0	26±5.8 years
Average paternal age	31.3±5.8	31±6.1 years

Table 4: Distribution of the cases analysed for cytogenetic studies (n=143)

	Down syndrome (n=110)	*Mental retardation and related disorders (n=33)*
Total number of cases	110 (76.9%)	33 (23.0%)
Number of males	75 (68.1%)	24 (21.8%)
Number of females	35 (31.8%)	9 (6.2%)
Cases with abnormal karyotype	95 (86.3%)	2 (6.0%)

In the present study, 110 (76.9%) cases were referred as Down syndrome cases and 92 (64.3%) of them showed regular trisomy (Table 1,2); 3 (2.0%) showed translocations. Down syndrome is the most common and the best-known chromosomal disorder in man. Most cases (~95%) have regular trisomy 21. At least 2% of patients of Down syndrome have been reported to have mosaicism with normal and trisomy 21 cell lines and about 3% of these cases have 46 chromosomes with an extra chromosome 21 being fused with one of the other acrocentric chromosomes (Mueller and Young 1998). Very rarely the partial trisomy of a short distal segment

Table 5: Details of the cases exhibiting microcephaly along with mental retardation

Case number	*Age and sex*	*Referred as*	*Microcephaly (+/-)*	*Karyotype*
446	5 years, Male	Delayed milestones	+	46,XY
615	1 year, Male	Microcephaly	+	47,XY,+21
R-63	16 days, Male	Congenital anomalies	+	46,XY
730	9 years, Female	Cerebral palsy	+	46,XX
736	8+ years, Female	Delayed milestones	+	46,XX
738	4 years, Male	Mixed cerebral palsy	+	46,XY
763	2 years, Female	Congenital anomalies	+	46,XX
767	5+years, Male	Developmental retardation	+	46,XY
R-68	3 years, Female	Microcephaly, micrognathia	+	46,XX
R-131	2+ years, Male	Delayed milestones	+	46,XY
R-205	3+ years, Female	Delayed development	+	46,XX
824	9 months, Male	Congenital anomalies	+	46,XY,del(18)(18q21.1-18q23)
843	14 months, Male	Congenital anomalies	+	46,XY

Table 6: Frequency and distribution of cases w.r.t. birth order within the sibship

Order in sibship	*Down syndrome (n=110)*	*Mental retardation and delayed milestones (n=36)*
1st	44 (40.0%)	14 (42.4%)
2nd	26 (23.6%)	12 (36.3%)
3rd	16 (14.1%)	2 (6.0%)
4th	9 (8.1%)	0
5th	6 (5.4%)	1 (3.0%)
6th	0	1 (3.0%)
7th	2 (1.8%)	0
8th	1 (0.9%)	0

of chromosome 21, including the bands q22-qter, results in Down syndrome (Delabar et al. 1993). This probably explains our 15 (10.4%) cases that showed normal chromosomal complement despite abnormal phenotype (Table 1,2). In these cases FISH analysis is being undertaken.

In the present study 33 cases (23.0%) were referred as having mental retardation, delayed milestones and congenital anomalies. Phenotypic and clinical examination of these cases showed microcephaly in 13 cases (9.0%) (Table 5). Two of these patients had abnormal karyotype i.e., 47,XY,+21 and 46,XY,del (18) (18q21.1-18q23). 11 cases with apparently normal chromosomal complement may have some monogenic abnormality or some complex structural rearrangements that are beyond the detection limits of routine G-banded chromosome analysis. Microcephaly, is characterized by a reduced brain volume and small skull associated with mental retardation, convulsions and other neurological symptoms. While some cases are due to monogenic abnormalities, the others may have been due to injuries during delivery or infections like rubella, cytomegalovirus or toxoplasmosis during early stage of pregnancy. Microcephaly can also be seen as one of the symptoms in several rare syndromes with monogenic background and in certain chromosomal anomalies (Gustavson 1996). It is estimated that 5-10% of all the cases of idiopathic mental retardation may have a small subtelomeric rearrangement (Slavotinek et al. 1999) but the number of patients that are identified with this etiology remains small.

Cytogenetically invisible unbalanced translocations have been reported to cause mental retardation syndromes. In all these syndromes, phenotypic characteristics, in addition to the mental retardation contribute to the recognition of the disorder and to the identification of the deletions (Holinski-Feder et al. 2000). M-FISH is able to detect cryptic translocations in supposedly normal metaphase spreads (Uhrig et al. 1999) and the screening of subtle structural anomalies can be done by using telomere-specific FISH probes. Due to high concentration of genes in telomeric region, specific probes could be very informative to investigate karyotypically normal individuals with non-specific MR and children with non-specific mild dysmorphic features. Molecular analysis in such cases will also be helpful in revealing the underlying mutations. MR cannot be cured but can be prevented. Hence it is important to ascertain the cause of mental retardation, so that recurrence risk can be reduced and where MR is transmissible, prenatal diagnosis and proper genetic counselling could be provided.

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