CHROMOSOMAL ABNORMALITIES IN A REFERRED POPULATION: A REPORT OF 383 IRANIAN CASES

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Abstract - This report presents the cytogenetic findings (G - banded chromosomal analysis) in 383 cases referred for suspected chromosomal abnormalities because of abnormal clinical features. Chromosomal aberrations were found in 63 (16.5%) of these cases, free trisomy 21 (7%) being the most common abnormality, followed by 47, XXY karyotype (4%). The breakdown figures for each group is discussed in the text. Acta Medica Iranica 36 (1): 64 - 69; 1998

Key words: Chromosome abnormality, Iranian population, GTG - banding technique, Down Syndrome, Klinefelter.

INTRODUCTION

Studies on chromosomal abnormalities in Iranian population are few and scanty. This study shows the frequency and incidence of major chromosomal abnormalities on the basis of clinical features, and demonstrates the value of cytogenetic investigation in patients who have abnormal clinical features since the rate of chromosomal abnormalities is significantly higher than in an unselected population.

MATERIALS AND METHODS

This survey comprises 383 cases referred to the Cytogenetic Division of the Medical Diagnostic Laboratory of the Pars Hospital at Tehran from 1993 to 1996. The patients were referred by practising physicians of a wide variety of disciplines. All cases were routinely evaluated by GTG banding (G bands by Trypsin Using Giemsa). C - banding was also utilized in cases where chromosomal heteromorphism with regard to constitutive heterochromatin regions were suspected. At least 10 metaphases were examined for each patient. In mosaic cases, 30 - 50 metaphase spreads were examined.

Photography was performed for the abnormal cases. ISCN (3) guidelines for chromosome nomenclature were followed.

RESULTS AND DISCUSSION

Of the 383 cases investigated, 63 had chromosome abnormalities (16.5%) (Table 1). The unusual chromosomal abnormalities have been summarized in Table 2. The chromosomal findings in different referred groups are discussed as follows:

Table 1. Referral categories with indication for chromosomal abnormalities

Clinical feature	Total	Karyotype	
	number	normal	abnormal(%)
Down syndrome	30	4	26(87)
Klinefelter syndrome			
male infertility	52	38	14(27)
microtestis	4	4	0(0)
Primary Amenohrrea (including Turner syndrome)	51	44	7(14)
Secondary Amenohrrea	6	6	0(0)
Ambiguous genitalia and Hermaphroditism	22	16	6(27)
Failure to thrive	28	26	2(7)
Mental Retardation	15	12	3(15)
Fetal Loss	170	167	3(1.7)
Others	5	3	2(40)
Total	383	320	63(16.5)

1. Down syndrome

There were 30 cases who had the clinical features of Down syndrome and 26 of these were found to be chromosomally abnormal (87%) . Of these 23 (88%) with free trisomy 21, 2 (8%) were mosaic and one (4%) was unbalanced Robertsonaian translocatian between chromosomes 14 and 21. Our data correlate well with previous reports (4, 5), apart from the mosaic cases (8%) which could be due to small sample size. The majority of our cases, 73%, were newborns, 23% were between one and 10 years of age and the rest were between 10 and 20 years of age. The sex ratio in our abnormal subjects is almost 3: 2 in favour of females. This finding is different from previously reported data in which male subjects are prevalant (3: 2) (6) and this could be due to small number of cases.

2. Klinefelter

Two groups of individuals were referred for cytogenetic study: the adult males with infertility and subfertility problems and juvenile males with microtestis. In total out of 56 referred cases 14 patients had chromosomal abnormalities (25%). 11 of abnormal cases (79%) showed typical 47,XXY Klinefelter karyotype, two were mosaic 46,XY/47, XXY (14%) and one case appeared to have a deleted Y at q11.2 region. Both rates of 47, XXY and mosaic karyotypes in this study correlate well with the published data (1, 7). In one of the mosaic cases, 46, XY normal cell line was more prevalent than the 47, XXY cell line and the patient was oligospermic, whereas in the other mosaic case where the 47 , XXY cell was dominant, the patient was azoospermic. Such an observation is also confirmed by Emery et al (8).

Table 2. Summary of Unusual Chromosomal Abnormalities in Referred Cases with Abnormal Clinical Features

Case	Sex	Age	Reason for Referral	Type of chromosome Abnormality
73 - 308	M	22M	Down syndrome	46,XY, der (14;21) (q10;q10), + 21
73 - 221	F	25Y	F.H.Down syndrome	47,XX,+ mar pat (bisatellited G - size marker chromosome
73 - 224	M	33Y	Male Infertility	46,X, del(Y) (q11.2 q11.2)
74 - 031	M	32Y	Ambiguous Genitalia	mos 45, X/46, XX
74 - 270	M	8Y	Ambiguous Genitalia	mos 46, XX/46, XY
73 - 331	M	8.5Y	Mental Retardation	mos 47, XY, + 8/46, XY
73 - 134	F	11Y	Mental Retardation	45, XX, der (15; 15) (p11.1?2 q12 or q13) de novo
73 - 233	M	16M	Mental Retardation	46,X,Yq+
73 - 096	F	18Y	Failure To Thrive	46,XX,r(4)
73 - 340	M	20M	Failure to Thrive	46, XY, der (4)t(4;6)(q35;q21),r(6)(p25q21)
74 - 106	F	17Y	Primary Amenorrhea	mos 45,X/46,X, psu idic (X) (q22)
74 - 192	F	16Y	Primary Amenorrha	46,X,del(X)(q13)
73 - 194	F	17Y	Primary Amenorrhea	mos 45,X/46,X,i(X)(q10)
74 - 114	F	28Y	Primary Amenorrhea	mos 45, X/46,XY
74 - 014	F	12Y	Turner Syndrome	mos 45,X/46,XX,del(X)(p11)
73 - 180	F	28Y	Spontaneous Abortions	mos 45, X/47, XXX/48, XXXX/46, XX
73 - 082	F	31Y	Spontaneous Abortions	mos 45,X/46,XX
73 - 185	F	34Y	Spontaneous Abortions	mos 45,X/46,XX

M = Month

Y = Year

Patient with the deleted Yq11.2 was azoospermic, had short stature with abnormal teeth. This corresponds well with the deletion of Yq11.2 region, the locus for spermatogenesis , height and tooth shape in males. However, fluorescence in-situ hybridization (FISH) and further molecular work is needed to confirm this deletion. All Juvenile microtestis cases had normal karyotype.

3. Primary and secondary Amenorrhea

51 patients were referred because of primary amenorrhea , including 5 with Turner stigmata. 7 cases (14%) had abnormal karyotypes (Table 3).

Table 3. Primary amenorrhea and Turner syndrome cases with abnormal karyotypes

Case	Karyotype
73 - 154	46, XY
73 - 194	mos 45, X/46, X, i(X) (q10)
74 - 014	mos 45, X/46, X, del(X) (p11)
74 - 106	mos 45, X/46, x psu idic (X) (q22)
74 - 114	mos 45, X/46, XY
74 - 192	46, X, del(X).(q13)
74 - 264	45, X

Only one of the Turner referrals, case 74 - 014 (20%) was abnormal. Two of the primary amenorrhea cases had 46,XY cell line (Swyer syndrome).

Case 74 - 114 had a masculine like body built with small uterus and ovaries, and raised FSH and LH levels. Her karyotype was mos 45, X/46, XY (mixed gonadal dysgenesis). The second case, 73 - 154 showed a 46, XY karyotype. All six patients referred for secondary amenorrhea had normal karyotype.

4. Ambiguous Genitalia and Hermaphroditism

There was a wide range of referral age for ambiguous genitalia and hermaphroditism ranging from newborns to adult patients of age 32 - 36. Six out of a total of 22 were karyotypically abnormal (27%) (Table 4).

Table 4. Ambiguous genitalia and hermaphroditism with abnormal karyotypes

Case	Rearing Sex	Age	Karyotype	Clinical Feature
73 - 110	F	20 Y	46, XY	? Hermaphroditism
73 - 193	F	33 Y	46, XY	Primary amenorrhea, absent uterus
73 - 210	M	$2\frac{1}{2}$ Y	46, XX	? absent testis
74 - 031	F	32 Y	46, X/46, XX	Hermaphroditism, large uterus, masculine hair distribution
74 - 069	F	36 Y	46, XY	sister of 73-193, Primary amenorrhea, absent uterus
74 - 270	M	8 Y	46,XX/46,XY	Cryptorchidism

Cases 69 - 74 and 73 - 193 were sisters both referred because of primary amenorrhea and absent uterus. Their karyotypes were 46, XY. It is possible that those sisters have androgen insensitivity syndrome, the pattern of inheritance being X-linked recessive. Our data suggest a high incidence of sex karyotype - phenotype mismatch amongst patients reffered for ambiguous genitalia and hermaphroditism.

5. Failure to thrive

Only two patients out of a total of 28 referred for failure to thrive were abnormal (7%).

Interestingly, both these cases had ring chromosome. One patient, an 18 year old female had a ring 4 chromosome and the other a 20 months old boy had a ring 6 chromosome with breakpoint at 6q21 and addition of q 6q21 ---> 6qter segment to one of chromosomes 4. It is a well recognized fact that ring patients have slow development and growth as was shown in these two patients. Ring syndrome patient due to high rate of cell death usually have growth retardation.

6. Mental Retardation

Twenty percent of referred non Down syndrome mentally retarded cases were abnormal

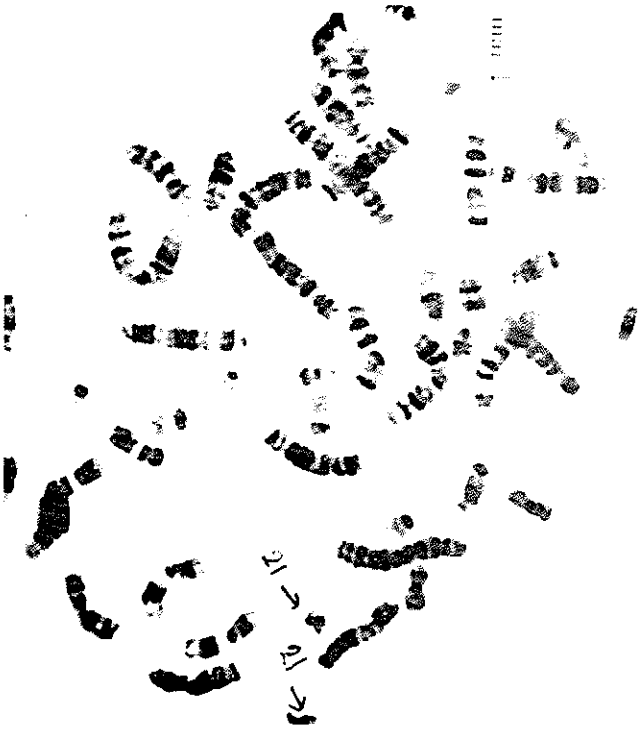

Fig. 1. The bisatellited G-Size paternal marker chromosome observed in a 25 years old healthy female referred for familial history of Down syndrome

Fig. 2. The deleted X-chromosome [46, X, del (X) (q13)] in a 16 years old girl with primary amenorrhea

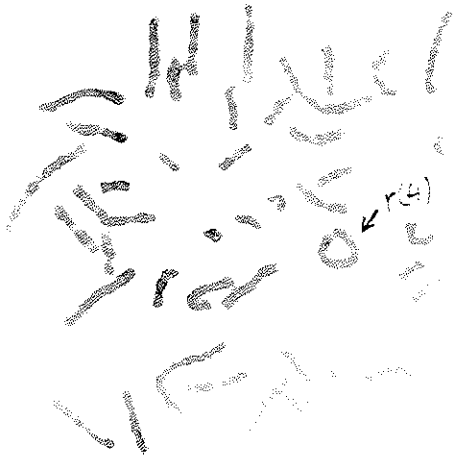

Fig. 3. The ring 4 chromosome [46, XX, r(4)] in an 18 years old female with failure to thrive

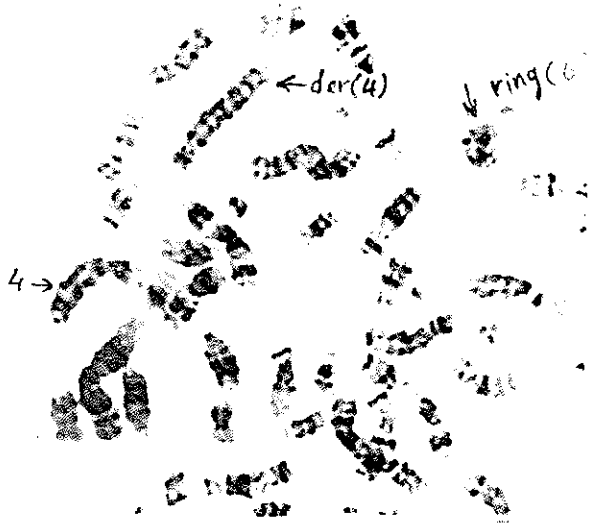

Fig. 4. A translocation between chromosome 4 and the distal part of the long arm of the chromosome 6 in a 20 months male referred for failure to thrive. The remaining chromosome 6 has formed a ring [46, XY, der (4)t (4; 6) (q35; q21), r(6) (p25 q21)]

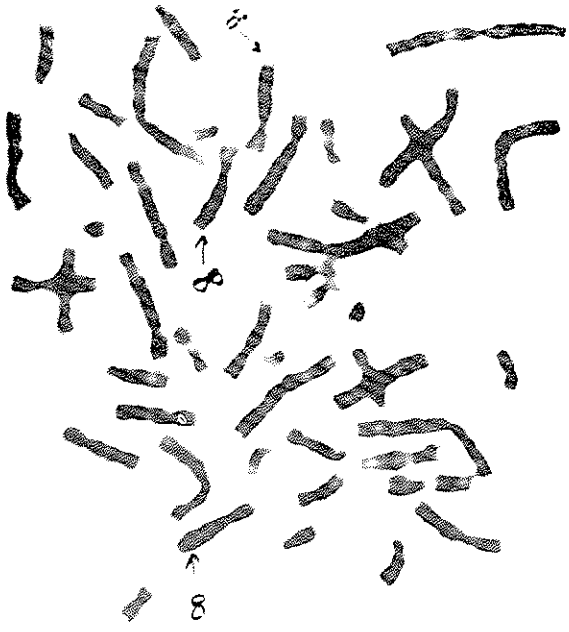

Fig. 5. The mosaic trisomy 8 (47, XY, +8/46, XY) in an 8.5 years old male referred for mental retardation

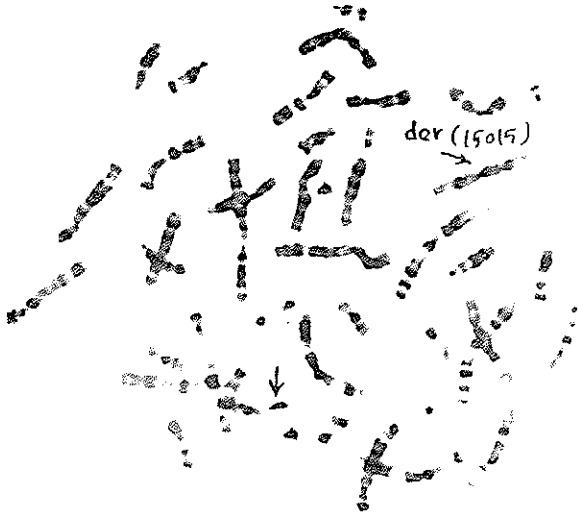

Fig. 6. A translocation of chromosome 15 {45, XX, der (15; 15)} in an 11 years old female reffered for mental retardation

(3 out of 15) (Table 1). Case 73 - 134 was an eleven years old female with ataxic movement, mental retardation and speech problems. She was found to have a translocation between two chromosmes 15 with breakpoints at p11.1 and q12~q13. The breakpoint at 15 q12~q13 corresponds to the locus for Angelman ~ Prader Willi syndromes. The phenotype of this patient was similar to Angelman syndrome. One could speculate that the gene interruption at 15q12~q13 could account for patient's phenotype. However, further moleculer and FISH studies are essential to verify the breakpoints.

7. Spontaneous Abortions

Out of 170 patients referred for spontaneous abortions , three were abnormal (2%). Two of these cases were mosaic 45, X/46, XX and the third case a 28 years lady who had a 45, X/46, XX/47, XXX/48, XXXX Karyotype.

8. Gthers

The two abnomal cases were a daughter and father both with a supernumerary bisatellited marker chromosome, referred to us because of family history of Down syndrome. The mother of the proband with marker chromosome and both parents of case 73 ~ 134 (t (15; 15)) were the remaining three cases of this group and all were normal. Figures 1 to 6 represent the metaphase spreads for some of the abnormal cases.

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