Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 23 (1), pp. 35–40 (1982)

A diagnostic survey of patients referred for chromosome analysis

G. Kosztolányi

Department of Paediatrics, University Medical School, Pécs

Out of 692 patients referred for chromosome analysis because of abnormal clinical features, 199 (28.7%) had chromosomal abnormalities. In addition, assessment of the abnormal phenotypic features and the data of other (laboratory, X-ray, etc.) examinations revealed 25 (3.6%) single gene disorders, 25 (3.6%) recognizable syndromes or associations of unknown aetiology, and in 4 cases (0.6%) environmental agents were established as possible aetiological factors. Altogether, of the 692 cases, 253 (36.5%) had a definitive diagnosis, while the remainder 439 were undiagnosed.

These results suggest that (*i*) chromosome analysis is worthwhile if the patient has significant clinical abnormalities, and (*ii*) a request for chromosome analysis should be viewed as one step in syndrome identification, so that a normal karyotype should stimulate the physician to further efforts to establish a diagnosis.

The present survey analyses the outcome of chromosome examinations of 692 referred cases (in and out-patients) over the eight-year period 1973–1980 in order to assess the contribution of chromosome analysis to the diagnosis of the malformed patients. The efficacy of our policy to establish diagnoses other than chromosomal aberration in patients referred for chromosome analysis is also evaluated.

Patients and Methods

During the 8-year period a total of 1048 chromosome examinations was carried out. Cases were classified into five groups: *A*) suspected of having chromosome anomalies, because of abnormal clinical features, 692 patients; *B*) children and adult family members of patients with chromosome aberrations or congenital malformations, 259 cases; *C*) adult volunteers, 38 cases; *D*) children screened by dermatoglyphic analysis, 39 cases; *E*) adult patients with chronic myelocytic leukaemia, 20 cases, with bone marrow examinations. In the following we shall deal only with group *A* (66% of the total of 1048 cases).

The majority of patients in group *A* were infants and older children referred by practising paediatricians for chromosome analysis. About a quarter of the cases were in-patients of our department.

All the karyotypes were analysed from lymphocyte cultures. At the beginning, G banding and other staining methods were used only where indicated, but in the last four years G and C banding was routinely carried out. A minimum of 12 metaphases were examined from each patient and

This work is dedicated to Professor Julius Mestyán on the occasion of his 60th birthday.

Supported by the Scientific Research Council, Hungarian Ministry of Health (3—23—1101—02—01 V).

the method of Bochkov et al. [1] was applied to exclude mosaicism. In addition, careful physical examinations were done repeatedly and further investigations (laboratory, X-ray, etc.) were carried out.

The results were assessed according to Winter et al. [7] with certain modifications. Cases were classified into groups according to the reason for referral. One of the following reasons for referral was usually given: 1. suspected chromosome abnormality specified by name; 2. multiple malformations; 3. children with odd-looking appearance and/or multiple minor anomalies; 4. single congenital (major or minor) anomaly; 5. mental retardation with no other malformation; 6. ambiguous genitalia or other sex anomalies; 7. miscellaneous (e.g. failure to thrive, dystrophy, etc.) including 9 cases with psychiatric disorders.

The final diagnoses were classified as 1. chromosome abnormalities; 2. single gene disorders; 3. recognized syndromes or associations of unknown aetiology; 4. environmental agents (e.g. serologically proved intrauterine infection, etc.). Cases with no chromosome aberration were classified into single gene disorders, recognised syndromes, or environmental agents only, when the physical features and/or the other findings strongly suggested the diagnosis in question. Patients undiagnosed at the time of chromosome analysis but subsequently given a diagnosis on reassessment at a later age are labelled by the final diagnosis.

TABLE I

Results of examinations of 692 patients referred for chromosome analysis because of abnormal clinical features

Reason for referral	No.	Abnormal karyotype	Single gene disorder	Syndrome or association of unknown aetiology	Environmental agent
Down syndrome	209	141 (67.5)			
Patau syndrome	11	5 (45.5)		1	
Edwards syndrome	17	8 (47.0)			
Mosaic 8-trisomy	2	1			
Cat eye syndrome	2				
Cri du chat syndrome	2	1			
Turner syndrome	38	17 (44.7)			
Klinefelter syndrome	19	6 (31.6)			
Multiple malformations	80	5 (6.2)	11 (13.7)	20 (25)	3
Odd-looking face and/or multiple minor anomaly	93	4 (4.3)	7 (7.5)	2	1
Single malformation or anomaly	40				
Mental retardation	54	1	1		
Ambiguous genitalia or other sex anomaly	64	7 (10.9)	6 (9.3)	1	
Miscellaneous	61	3			
Total	692	199 (28.7)	25 (3.6)	25 (3.6)	4 (0.6)

Results and Discussion

Of the 692 cases referred to us because of abnormal phenotypic features, 199 or *28.7%* had chromosomal abnormalities (see Table I). This frequency was similar to that observed in other studies [3, 5, 6]. Surprisingly, a higher rate of chromosomal abnormalities was found in females (32.5%) than in males (25.8%). A similar observation was reported by Singh [5] without any interpretation. These two data raise the question of a difference in the incidence of chromosome anomalies between males and females. This seems unlikely, especially as in the eight-year period we found chromosomal abnormalities in 102 males and 97 females, thus practically in equal number. More than twice as many males than females were, however, referred for chromosome analysis because of dysmorphic clinical features resulting in a difference in frequency between males and females observed. Therefore, the question is, are there more males than females with dysmorphic phenotype but normal chromosomes. Our observation and that of Singh [5] suggest that dysmorphic clinical features might be a slightly stronger indication for chromosome analysis in females than in males.

There were 209 patients who had the clinical features of *Down syndrome*. In 140 of these (66.9%) the initial suspicion was confirmed by the chromosome analysis. Of those referred because of suspected Down syndrome, only one out of the 209, a male infant with a small metacentric chromosome (47, XY, +mar) was given a definitive diagnosis other than 21-trisomy. All cases finally diagnosed as having 21-trisomy were referred with this diagnosis. Of the 140 cases with confirmed Down syndrome, ten (7.1%) were due to translocation (one D/G, one G/G, five 14/21, three 21/21), while three (2.1%) displayed a mosaic pattern.

Thirty-four cases were referred because of suspected *specific autosomal abnormalities* other than Down syndrome. About half of them had the specific chromosomal abnormality. Of the 11 cases referred because of suspected *Patau syndrome*, five were confirmed by chromosome analysis (one of them was due to translocation), while one infant had holoprosencephaly anomalad with normal karyotype. In one case finally diagnosed as having 13-trisomy, the specific diagnosis was not suggested by the referring clinician; the reason for referral was "multiple malformations".

Of those referred because of suspected *Edwards syndrome*, the clinical diagnosis could be confirmed in 7 out of 11 females, and in one out of 6 males, in accordance with the known preponderance of females to males in Edwards syndrome. Of these, two were mosaic normal/+18.

Out of 38 cases of suspected *Turner syndrome*, 17 (44.7%) had chromosomal abnormalities (of these, five had mosaic pattern). Apart from these 17 cases, two further cases, a newborn referred because of multiple malformations, and a 4-month-

old infant with ambiguous genitalia, were found to have a XO karyotype. Of those referred because of suspected Turner syndrome, only one case—an infant with Klippel-Feil anomalad—was given a definitive diagnosis other than Turner syndrome.

Out of 19 cases referred because of suspected *Klinefelter syndrome*, six (31.6%) had the specific chromosomal abnormality.

The 80 cases referred for chromosome analysis because of *multiple malformations* had a variety of "final diagnosis". Detailed diagnoses are given in the Appendix. Chromosomal abnormalities accounted for 6.2% of the group. In about two-fifths of the 80 cases a recognizable syndrome or association could be diagnosed, due to a single gene defect or of unknown aetiology. In three infants, environmental agents (two cytomegalovirus infections and one maternal diabetes) were the most probable aetiological factors responsible for the congenital abnormalities.

Of the 93 children referred because of *odd-looking face* and/or *multiple minor anomalies*, four (4.3%) had chromosome abnormalities, seven (7.5%) recognizable syndromes, while one case was diagnosed as fetal alcoholic syndrome (see Appendix).

No chromosomal abnormality could be observed in patients with single malformation or minor anomaly.

In the *mental retardation* referral group, one chromosomal aberration, a balanced 13/15 translocation, was found among the 54 cases. Although the aetiological role of this chromosomal abnormality is questionable, this was the only abnormal finding in this patient. In one referred case, a 2.5-year-old girl, Sanfilippo disease was finally diagnosed.

Of the 64 cases referred because of *ambiguous genitalia or some other sex anomaly*, seven had chromosomal abnormalities (2 XY/XO mosaicisms, 1 each XY/XX, XX/XXX, XY/XXY mosaicism, and 1—1 XO, XXXXY aneuploidy). Six further cases were diagnosed as single gene disorders, three adrenogenital syndromes, and three testicular feminisations, while in one boy referred because of cryptorchidism, the clinical features suggested the diagnosis of Noonan syndrome.

In the *miscellaneous* group, chromosomal abnormalities could be observed in three (two Yq deletions, one XYY) out of the 9 cases with psychiatric disorders.

Thus, of the 692 cases referred because of suspected chromosomal abnormalities, 28.7% had chromosomal aberrations, 3.6% single gene disorders, 3.6% recognised syndromes or associations of unknown aetiology, and in 0.6% of the cases environmental agents were the probable cause of congenital abnormalities. Altogether, of the 692 cases, 253 (36.5%) were given a definitive diagnosis, the remainder being classified under idiopathic congenital (major or minor) abnormalities, idiopathic mental retardation, or undiagnosed odd-looking babies.

Conclusions

Of the 692 cases with suspected chromosomal abnormalities, 28.7% had chromosomal aberrations. This high rate, comparing it to the 0.6% frequency of chromosomal aberrations in unselected newborn populations [2], demonstrates the diagnostic importance of cytogenetic examinations. Chromosome analysis is always indicated if the patient has significant clinical abnormalities. Our results, like those of others, also point to the low efficiency of karyotyping in patients with single malformations or mental retardation.

Generally, in 65—70% of congenital abnormalities the cause is unknown, and in the rest, genetic or preconceptual causes account for about 20%, chromosome or conceptual (cell division) causes for 3—5%, and known environmental (postconceptual) causes for 7—10% [3]. Although our cases cannot be regarded as a representative sample of congenital abnormalities in the population, it seems that in our material the percentage contribution of preconceptual (genetic) and environmental causes was low as compared to the total number of diagnosed cases. This would suggest that chromosome analysis should be regarded as one step in a general process of syndrome identification, so that a normal karyotype should stimulate the physician to further efforts to arrive at a reliable diagnosis.

Appendix

Classification of patients according to final diagnosis

I. Cases referred for multiple malformations

No.	Final diagnosis
	Chromosomal abnormalities:
1	46, XY, 6r
1	47, XYY
1	45, XO
1	46, XX, —13, +t(13q13q)
1	49, XXXXY
	Single gene disorders:
2	Holt–Oram syndrome
2	oral-facial-digital syndrome
1	achondroplasia syndrome
1	Smith–Lemli–Opitz syndrome
1	Laurence–Moon–Biedl syndrome
1	diastrophic dwarfism syndrome
1	Carpenter syndrome
1	Ellis–van Creveld syndrome
1	Jeune thoracic dystrophy syndrome
	Syndromes or associations of unknown aetiology:
6	VACTERL association
4	neural tube defect
2	Klippel–Feil anomalad
2	Goldenhar syndrome
1	Klippel–Trenaunay syndrome
1	Larsen syndrome
1	Beckwith–Wiedemann syndrome
1	ADAM syndrome
1	Robin anomalad
1	arthrogryposis
	Environmental agents:
2	congenital cytomegalovirus infection
1	maternal diabetes

II. Cases referred because of odd-looking face and/or multiple minor anomalies

No.	Final diagnosis
	Chromosomal abnormalities:
1	46, XX, 18p—
1	46, XX, 4r
1	45, XO

1 46, XX, 21r

Single gene disorders:

3 Saethre–Chotzen syndrome
1 ectodermal dysplasia
1 Albright syndrome
1 Seckel syndrome
1 Cockayne syndrome

Syndromes of unknown aetiology:

1 Silver–Russel syndrome
1 Cornelia de Lange syndrome

Environmental agents:

1 fetal alcoholic syndrome

References

1. Bochkov NP, Kuleshov NP, Chebotarev AN, Alekhin VI, Midian SA: Population cytogenetic investigation of newborns in Moscow. Humangenetik 22:139, 1974
2. Kosztolányi G: Cytogenetic screening of newborns. (in Hungarian) Magy Pediatr 11 : 137, 1977
3. Méhes K, Bajnóczky K: Incidence of major chromosomal abnormalities. Clin Genet 19:75, 1981
4. Scrimgeour JB, Cockburn F: Congenital abnormalities. Lancet 2:1349, 1979
5. Singh DN: Cytogenetic study of individuals suspected of chromosome anomalies. Clin Pediatr 16:619, 1977
6. Verma RS, Dosik H: Incidence of major chromosomal abnormalities in a referred population for suspected chromosomal aberration: a report of 357 cases. Clin Genet 17:305, 1980
7. Winter RM, Ridler MAC, McKeown JA: A diagnostic survey of infants referred for chromosome analysis in the neonatal period. Br Med J 281:1045, 1980

Received October 5, 1981

G. Kosztolányi, MD
József A. u. 7.
H-7623 Pécs, Hungary