Chromosomal aberrations in children with suspected genetic disorders

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زيغ الصبغيات في الأطفال المصابين باضطرابات وراثية مشتبهة

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خلاصة : تمت دراسة النمط النووي لخلايا 137 طفلا يشتبه في إصابتهم بشذوذات صبغية ، مثل المتلازمات الوراثية غير المؤكدة ، والتشوهات الخلقية المتعددة ، وقصر القامة ، وتشوه الملامح ، والتخلف العقلي غير المصنف ، ومتلازمة داون . ولقد وُجد شذوذ في النمط النووي في عدد مجموعه 53 حالة (38.7%) تفصيلها كما يلي : تثلث بالصبغي 21 (36 حالة ، 26.3%) وتثلث بالصبغي 18 (3 حالات ، 2.2%) ، وتثلث بالصبغي 13 (حالة واحدة ، 0.7%) ، واختلال جزئي في صيغة الصبغيات الجسدية (5 حالات ، 3.6%) ، وانقلاب للداخل حول مركز الصبغي التاسع (حالتان ، 1.5%) ، ووجود صبغي واسم (حالتان ، 1.5%) ، وزيغ في الصبغيات الجنسية (4 حالات ، 2.9%) . ولقد أبدت كل هذه الحالات تغايرا في النمط الظاهري للجينات الخلوية . يستخلص من هذه النتائج أن تحليل الجينات الخلوية مفيد في استقصاء حالات الأطفال المصابين باضطرابات وراثية مجهولة المنشأ لتأكيد التشخيص السريري وضمان تقديم النوعية الوراثية الصحيحة .

ABSTRACT Karyotyping was done in 137 children suspected of having chromosomal abnormalities such as genetically uncertain syndromes, multiple congenital anomalies, short stature, dysmorphic features, unclassified mental retardation and Down syndrome. A total of 53 (38.7%) had an abnormal karyotype: trisomy 21 (36; 26.3%), trisomy 18 (3; 2.2%), trisomy 13 (1; 0.7%), partial autosomal aneuploidy (5; 3.6%), pericentric inversion of chromosome 9 (2; 1.5%), marker chromosome (2; 1.5%) and sex chromosome aberrations (4; 2.9%). All of them showed phenotypic–cytogenetic heterogeneity. These findings suggest that cytogenetic analysis is useful in the investigation of children with genetic disorders of unknown origin to confirm clinical diagnosis and to allow for proper genetic counselling.

Les aberrations chromosomiques chez les enfants suspects de troubles génétiques

RESUME Un cariotype a été réalisé chez 137 enfants suspects d'anomalies chromosomiques telles les syndromes génétiquement incertains, les anomalies congénitales multiples, le retard statural, les traits de dysmorphie, l'arriération mentale non classifiée et le syndrome de Down. Au total, 53 enfants avaient un cariotype anormal: trisomie 21 (36; 26,3%), trisomie 18 (3; 2,2%), trisomie 13 (1; 0,7%), hétéroploïdie autosomique partielle (5; 3,6%), inversion péricentrique du chromosome 9 (2; 1,5%), marqueur chromosomique (2; 1,5%) et aberrations des chromosomes sexuels (4; 2,9%). Tous présentaient une hétérogénéité phénotypique et cytogénétique. Ces résultats laissent penser que l'analyse cytogénétique est utile dans les investigations réalisées chez les enfants ayant des troubles génétiques d'origine inconnue afin de confirmer le diagnostic clinique et de permettre le conseil génétique approprié.

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Introduction

There are over 100 chromosomal syndromes which have been reported. While on an individual basis many of these are rare, together they make a major contribution to human morbidity and mortality [*1*].

The impact of chromosomal abnormalities is greatest during fetal life when they have their highest frequency and represent a major cause of fetal loss [2]. The frequency of various chromosomal abnormalities is quite different in neonates (0.7%) as compared to abortuses (about 50%), since some aneuploidies are lethal *in utero* [*3*].

The major autosomal abnormalities share a number of phenotypic features that are not distinctive or specific, including mental retardation, cardiac malformation and growth deficiency. While there is variability within every cytogenetic syndrome, neonatal death and serious congenital malformations are frequent manifestations. Most of the specific cytogenetic syndromes have a constellation of features that distinguish them and allow the clinician to suspect the condition [*2*].

Several studies have shown documented chromosomal abnormalities among unselected populations of neonates and older children [*4*]. Other cytogenetic studies among selected populations with abnormal phenotype features have also been conducted [*5,6*]. The frequency of chromosomal abnormalities is known to be significantly higher in selected populations than in unselected populations [*7,8*].

The aims of the present work were to investigate the different types of chromosomal aberrations and their relative frequencies in a group of children with suspected genetic disorders and to identify precisely the role of cytogenetic investigation in confirming the diagnosis, thus allowing proper genetic counselling to be offered.

Patients and methods

The study included 137 children with various phenotypic abnormalities such as genetically uncertain syndromes, multiple congenital anomalies, short stature, dysmorphic features, unclassified mental retardation and Down syndrome. Their ages ranged from one month to nine years. They were selected from the outpatient clinic of the Human Genetics Department, Medical Research Institute, Alexandria University. All the patients were subjected to a full genetic study; complete genetic examination and pedigree construction was done to exclude known nonchromosomal causes of anomaly. Cytogenetic analysis was carried out for all the patients. The study included peripheral lymphocyte culture by a standard method using the G-banding technique according to Seabright [*9*]. At least 30 metaphases were scored for each patient. Three cells were karyotyped. Usually the total chromosome count was determined in 10–15 cells, but if mosaicism was suspected then 30 or more cell counts were undertaken [*10*].

Results

Of the 137 patients on whom chromosomal analysis was done, chromosomal aberrations were detected in 53 patients (38.7%); of these, 49 (35.8%) involved autosomes, while only 4 (2.9%) involved gonosomes.

Ninety-seven per cent of the cases (40/41) referred as having a known chromosomal syndrome were aneuploid; 13% of the remaining (13/96) with suspected chromosomal disorders had an abnormal karyotype (Table 1).

Forty patients had autosomal trisomy; trisomy 21 was detected in 36 patients (67.9% of the cytogenetically abnormal

cases), which formed the majority. Among those, 88.9% had free trisomy 21, 8.3% had translocation trisomy 21 and 2.8% had mosaic trisomy 21.Three patients had trisomy 18 and one had trisomy 13 (Tables 2 and 3; Figures 1, 2 and 3).

Five patients (3.6%) had partial autosomal aneuploidy: one had 46,XY,del(5)(p14); one had 46,XY,add(5)(q35.3); one had 46,XY,del(10)(q26.2q26.3); one had 46,XY,add(12)(p13.3); and the last one had 46,XY,add(15)(q26.3). (Tables 2 and 3; Figure 4A, B and C).

Table 1 **Genetic disorders in patients referred for cytogenetic studies**

Suspected genetic disorder	Number of patients referred	Number of patients cytogenetically abnormal
Down syndrome	36	36
Edwards syndrome	4	3
Patau syndrome	1	1
Mental retardation/dysmorphic features/congenital anomalies/short stature of unknown cause in females	96	13
Total	137	53

Table 2 **Abnormal karyotypes**

Karyotype	Phenotype	Number of cases
47,XY,+21	Down syndrome	19
47,XX,+21	Down syndrome	13
46,XY, t(13;21)	Down syndrome	1
46,XY, t(14;21)	Down syndrome	2
47,XY,+21/46,XY	Mosaic Down syndrome	1
47,XX,+18	Edwards syndrome	3
47,XY,+13	Patau syndrome	1
46,XY,del (5)(p14)	Mental retardation	1
46,XY,add (5)(q35.3)	Dysmorphic features	1
46,XY,del (10)(q26.2q26.3)	Mental retardation	1
46,XY,add (12)(p13.3)	Congenital anomalies	1
46,XY,add (15)(q26.3)	Mental retardation	1
46,XY,inv (9)(p11)	Dysmorphic features	1
46,XY,inv (9)(p11)	Mental retardation	1
47,XX,+mar/46,XX	Congenital malformations	1
47,XY,+mar/46,XY	Congenital malformations	1
45,X	Turner syndrome	2
45,X/46,XX	Mosaic Turner syndrome	2
Total		53

Table 3 **Categories and frequency of the chromosome abnormalities identified**

Category	Number of cases	%
Trisomy 21 (Down syndrome)	36	26.3
Trisomy 18 (Edwards syndrome)	3	2.2
Trisomy 13 (Patau syndrome)	1	0.7
Partial autosomal aneuploidy	5	3.6
Inversion (pericentric) of chromosome 9	2	1.5
Marker chromosome	2	1.5
Monosomy X (Turner syndrome)	2	1.5
Mosaic Turner syndrome	2	1.5
Normal	84	61.3
Total	137	100

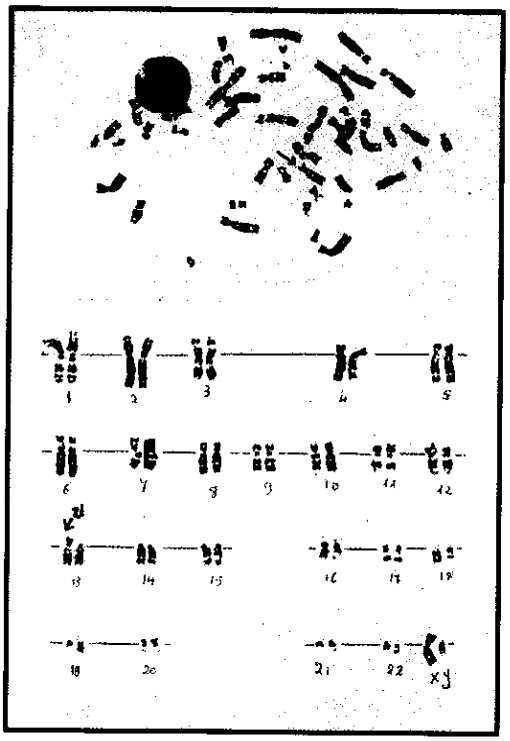

Figure 1 **Male karyotype showing translocation (13;21)**

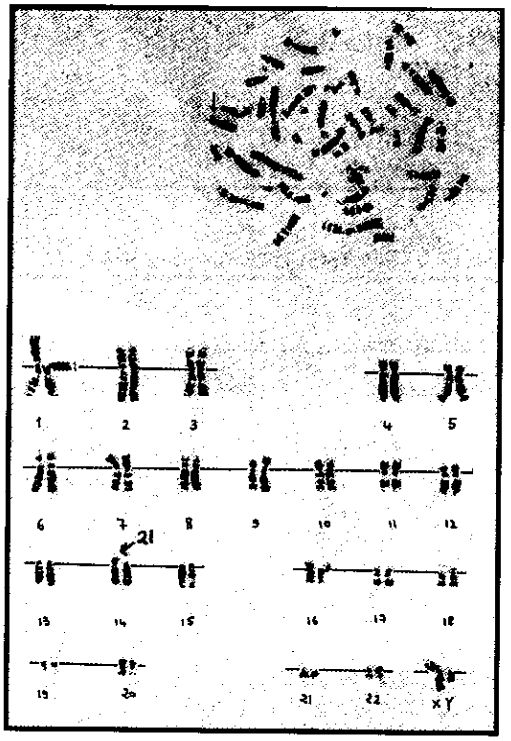

Figure 2 **Male karyotype showing translocation (14;21)**

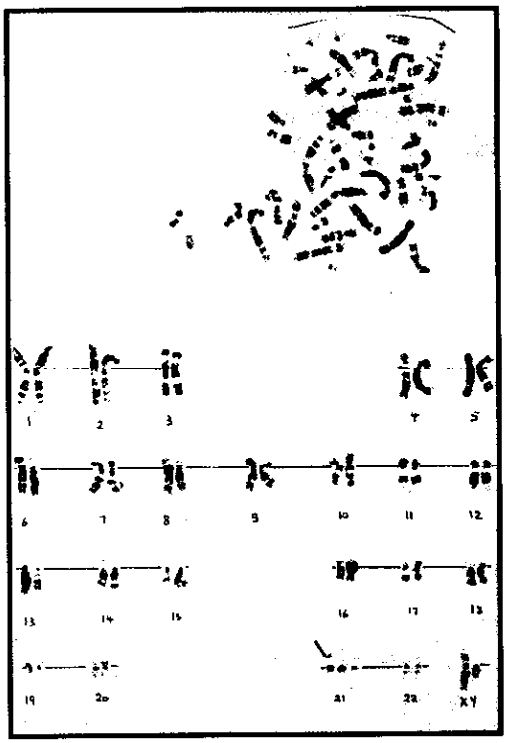

Figure 3 **Male karyotype showing trisomy 21**

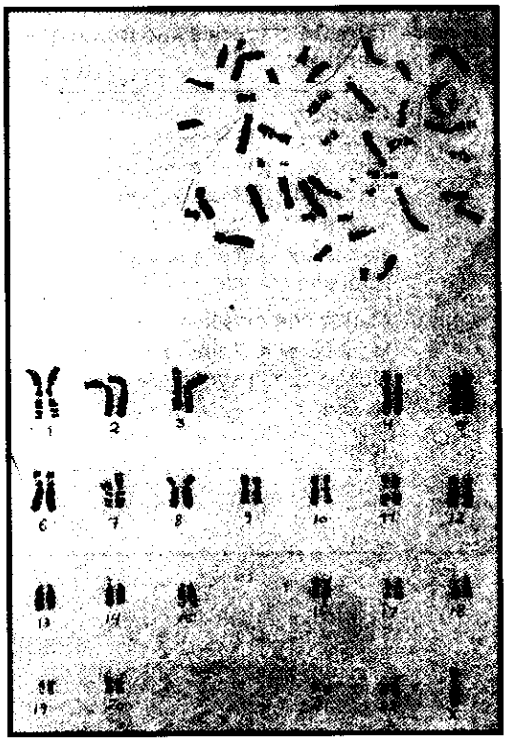

Figure 5 **Female karyotype showing monosomy X (Turner syndrome)**

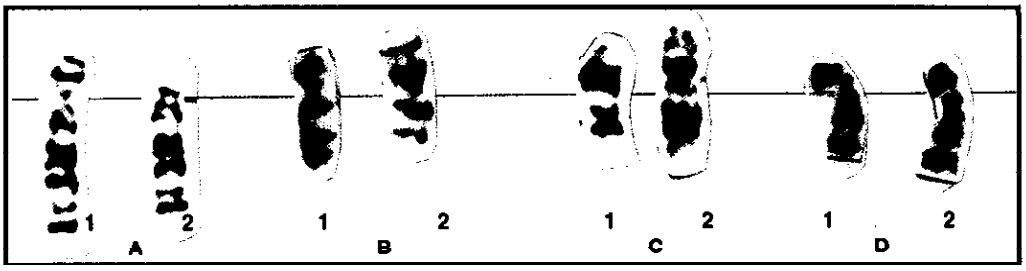

Figure 4 **Partial karyotype showing:**
A (1): normal chromosome 5
A (2): del (5) (p14);
B (1): normal chromosome 10
B (2): del(10)(q 26.2q26.3)
C (1): normal chromosome 12
C (2): add (12) (p13.3)
D (1): normal chromosome 9
D (2): pericentric inversion of chromosome 9

Two patients (1.5%) had pericentric inversion of chromosome 9. The patient referred with dysmorphic features was 46,XY,inv(9)(p11) and the patient with mental retardation was 46,XY,inv(9)(p11) (Tables 2 and 3; Figure 4D).

Two patients (1.5%) had mosaic supernumerary marker chromosome: the girl who had been referred with congenital malformations was 47,XX+mar/46,XX; the infant who was also referred with congenital malformations was 47,XY+mar/46,XY. In each patient the exact nature of the marker chromosome could not be identified. The parents were also subjected to chromosomal analysis but the marker was not present (Tables 2 and 3).

Four patients (2.9%) had sex chromosome aberrations; two girls referred with short stature were monosomic X (45,X) and two girls referred with dysmorphic features were mosaic Turner (45,X/46,XX) (Tables 2 and 3; Figure 5.).

Discussion

In consecutive neonatal studies, autosomal abnormalities are usually as common as sex chromosome aberrations [*11*]. In studies based on a referred population with phenotypic abnormalities, such as the present work, autosomal abnormalities (35.8%) are much higher than those of the gonosomes (2.9%). This figure is in agreement with other surveys [*12,13*].This is mainly due to the fact that sex chromosome imbalance has a much less deleterious effect on the phenotype than does autosomal aneuploidy [*11*].

There are wide variations in the frequency of chromosomal aberrations in individuals suspected of having genetic disorders as reported by different investigators [*7,8*]. Berry et al. studied 114 patients and found chromosomal aberrations in 18 (15.8%) [*14*]. Navsaria et al. evaluated 1000 patients and found chromosomal aberrations in 160 (16%) [*15*]. Al-Awadi et al. studied 472 patients and found 92 cases (19.5%) [*16*]. Al-Arrayed reported a frequency of 27% among 500 patients [*17*], Verma and Dosik found a frequency of 27.1% among 357 patients [*6*] and Singh reported a frequency of 28.8% among 451 patients [*5*].

In the present work, chromosomal aberrations were detected in 38.7% of the cases with suspected genetic disorders. This figure is higher than in most of the previously mentioned studies. A similar higher frequency (40%) of chromosomal abnormalities was reported by Kenue et al. among 120 patients [*13*]. This may be due to the small sample size.

Among patients with no known chromosomal syndrome in the present study, 13.5% (13/96) were karyotypically abnormal. This frequency is in agreement with Kenue et al. [*13*]; however, it was much higher than that observed in unselected populations [*4*].

Trisomy 21 has been recognized for more than 100 years. Because it is a common and familiar disorder, Down syndrome has been studied much more thoroughly than other chromosomal disorders. The Down syndrome phenotype is due to a triple amount of chromosome 21 [*11*]. The frequency of Down syndrome in patients with abnormal chromosomes in the present study was 67.9%. This value was similar to other surveys [*12,13*]. This could be attributed to its easy detection at the clinical level.

The frequency of standard trisomy 21 amongst Down syndrome patients in the present study was 88.9%. This value is in agreement with other surveys which ranged from 84.6% to 95% [*11*]. The frequency of

mosaicism in Down syndrome patients is reported to vary between 0% and 4%. Only 2.8% of patients with Down syndrome in the present study had mosaic Down syndrome. The frequency of translocation involving chromosome 21 among patients with Down syndrome in the present study was 8.3%. This figure is higher than previous reports (5.6% [*18*], 5.2% [*19*], 6.81% [*20*]), but the actual level depends on the maternal age distribution and the rate of indication for prenatal diagnosis [*21*].

Although individually rare, partial autosomal aneuploidies are the second most common chromosomal abnormality after trisomy 21 [2]. Our results (3.6%) confirm this finding but the frequency found in our study is higher than that reported by Kenue et al. (0.8%) [*13*] and Al-Awadi et al. (0.3%) [*16*]. It is believed that excess or loss of several contiguous genes along the chromosome involved will explain the phenotypes of these conditions.

Most of the pericentric inversions observed in humans do not in themselves give rise to any specific phenotypic abnormalities. However pericentric inversion has been found to be associated with infertility, repeated fetal loss, congenital anomalies and mental retardation [*11*,*22*]. With regard to the two cases with pericentric inversion detected in the present study, one had been referred with mental retardation while the other had congenital anomalies. Pericentric inversion has been implicated as a possible predisposing factor for nondisjunction and interchromosomal effect [*22*].

Marker chromosomes are defined as abnormal chromosomes that cannot be fully characterized based on standard cytogenetic analysis [*23*]. The incidence of marker chromosomes has been found to be 0.024% among neonates [*24*]. The association of an additional marker chromosome and abnormal phenotype has been described by Ballesta et al. in 14 probands with mental retardation and malformations [*25*]. The two patients with a marker chromosome detected in the present study had been referred with congenital malformations but the precise origin of the markers could not be determined using available techniques.

The incidence of Turner syndrome in consecutive neonates has been reported to be 0.04% [*13*]. Turner syndrome is one of the few chromosomal aberrations that can be recognized clinically during infancy or childhood based on short stature, broad shield chest, lymphoedema of the lower limbs, webbed neck and multiple minor anomalies [*26*]. However, karyotyping is necessary to confirm the diagnosis. The present study included four (2.9%) patients with Turner syndrome. Their chromosomal patterns were variable; 45,X (two cases) and 45,X/46,XX (two cases). This frequency agrees with Kenue et al. (2.5%) [*13*] but it was lower than that reported by Guera et al. (18%) [*27*].

Conclusion

Among a group of children with phenotypic abnormalities, the frequency of autosomal chromosomal aberrations was found to be much higher than sex chromosome anomalies. Trisomy 21 and partial autosomal aneuploidy were the most frequent. The precise delineation of a major autosomal trisomy is only possible using clinical examination and cytogenetic tools. Recognition of parents with chromosomal abnormalities is important as the risk of recurrence is high in some cases. This knowledge allows proper genetic counselling to be provided.

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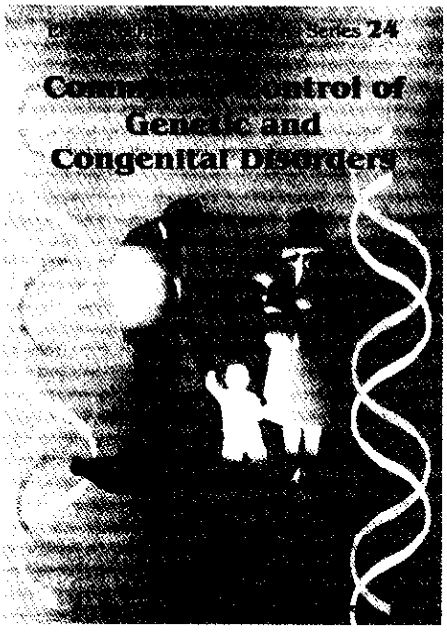

Who is the target audience?

This publication is aimed at health policy-makers and health professionals, particularly those concerned with the prevention, control and management of congenital and genetic disorders.

Why has this book been written?

This publication critically reviews the data available on the epidemiological characteristics of congenital and genetically determined disorders and evaluates their present magnitude within the Eastern Mediterranean Region. It aims to increase awareness of these disorders as an issue of growing concern to public health. Feasible public health intervention is discussed, with emphasis on the role of primary health care. A structure and guidelines for the establishment of prevention and control programmes within existing health care systems are proposed.

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