Global Journals Inc.

GLOBAL JOURNAL OF MEDICAL RESEARCH: F
DISEASES
Volume 19 Issue 6 Version 1.0 Year 2019
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Cytogenetic Findings in Children with Postnatal Growth Retardation

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Design and Methods: This was the largest study to date in children with PGR in Turkey, and presented the cytogenetic characteristics of 362 patients diagnosed with age range from 1 month to 18 years as having with PGR in a 17 years. The standard protocol for peripheral blood lymphocyte culture was followed by metaphase chromosome preparation and conventional analysis of G-banded chromosomes.

Results: The CAs were detected in 8,0% of 362 patients. The median age at diagnosis was 6,3 years in children. The incidence of abnormal karyotype was higher in females than that of males (the female-male ratio=2.2). The 5,0% of these CAs were structural aberrations, and also numerical aberrations were 3,0%.

Keywords: *postnatal growth retardation; cytogenetic; chromosomal aberrations.*

GJMR-F Classification: *NLMC Code: WQ 500*

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Cytogenetic Findings in Children with Postnatal Growth Retardation

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Conclusion: This study showed that some anomalies detected in PGR patients had shown correlations clinical characteristics of the patients. But, some of them are newly found and need to be investigated. Turner syndrome with various forms of chromosomal complement is the most common chromosomal abnormality causing growth failure in girls: This information could contribute to an understanding of the role of chromosomal changes in PGR.

Keywords: postnatal growth retardation; cytogenetic; chromosomal aberrations.

I. Introduction

Growth retardation can be defined as the failure of the child to show growth appropriate to his or her age and gender. For normal growth, the growth factors and genetic structure of the individual must be healthy. Generally, growth before birth is closely related to the environment in which the baby lives, that is to say, the mother's health, nutrition, and disease. Postnatal growth after intrauterine growth retardation (IUGR) depends on the cause of growth retardation, postnatal nutritional intake, and social environment. IUGR affects 3-10% of pregnancies; 20% of stillborn infants have IUGR. Perinatal mortality rates are 4-8 times higher for growth-retarded infants, and morbidity is present in 50% of surviving infants. There is a strong association between IUGR, CAs, and congenital malformations. It is thought that an abnormal fetal karyotype is responsible for approximately 20% of all IUGR fetuses, and the percentage is substantially higher if growth failure is detected before 26 weeks' gestation (1). Fetuses with chromosome disorders are frequently growth restricted (the common trisomies of chromosomes 13, 18 and 21), and suboptimal growth is also reported for many autosomal abnormalities such as duplications, deletions and ring chromosomes. Furthermore triploidy with unbalanced chromosome translocations and deletions are also common genetic events (2–4). In a recent study, CAs was found in 15,0% of the children with postnatal growth retardation (5). The present study was also aimed to detect various CAs in Turkish population using conventional cytogenetic analysis in children with postnatal growth retardation.

II. Materials and Methods

We present the cases with postnatal growth retardation, developmental delay, and other anomalies with growth retardation; unable to walk, to not speak, unable to sit, incontinence, eating difficulties, handles short, epilepsy, mental retardation, cerebral atrophy, dysmorphism, goiter, turners, and amenorrhea. This is a prospective observational study of patients who were newly diagnosed with PGR and presenting to the Pediatric Clinic, Faculty of Medicine, Çukurova University, The initial diagnosis of PGR as made by the referring clinical pediatric, based on the available clinical details. Turkey. A total of 362 patients (183 males and 179 females), with a median age of 6,3 years (range 1 monthly-18 years), and the sex ratio (male/female) 1,02 were referred to our genetics laboratory. Cytogenetic analysis was performed using a conventional G banding technique. Cytogenetic analysis of blood samples was performed in the Cytogenetics Laboratory, at the Department of Medical Biology and Genetics, Faculty of Medicine, Çukurova University. Karyotypes were documented according to the International System for Cytogenetic Nomenclature (ISCN) recommendations (6). At least 20 metaphases were karyotyped.

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III. Results

Cytogenetics was performed in 362 patients diagnosed with PGR. The male-female ratio was 1,02, and the median age at diagnosis was 6,3 years. The incidence of abnormal karyotype was higher in females (n=20, 69,0%) than that of males (n=9, 31,0%) (The female-male ratio=2,2). Here we report only on the identified cytogenetic anomalies. Out of 362 patients, 29 (8,0%) were found to have abnormal karyotype and the rest of 333 (92,0%) were normal. The CAs were shown in Table 1.

The structural aberrations (translocations, deletions, inversions, isochromosome and fragilities) and numerical aberrations were 5,0% and 3,0%, respectively. Especially, translocations are the most common karyotype (1,4% and 5 cases) among the patients, followed by t(6;11) (q25;q23); t(16;19) (q24;p11); t(5;12) (q34;p12); t(8;7) and robt(14;21). The ratio of inversions in all CAs was 1,1% (4 cases) [inv(14) (q13;q24); inv(9) (p12;q21); inv(9) (p12;q21); inv(9) (p11;q13)]. The deletions were present in approximately 0,6% of children [(del(5p13); del(18) (p13)]. Isochromosomes were present in 2 (0,6%) patients [Xi(Xq); 45, X/46, Xi(Xp)]. The ratio of fragilities were 0,8% of all patients [fra (8p23); fra (5q24); fra(13q32)]. Among numerical CAs, 11 patients (3,0%) had aneuploidies (XX,+21; XY,+21; XX,+21; 46,XX/47, XX+21; +mar; 45,X; 45,X; 45,X; 45,X; 45,X; 45,X/46,XX). (Table 1).

Table 1: Characteristics of the patients and the results of karyotypes

Sex/Age	Karyotypes	No. of cases	Frequency in all cases (%)
	Normal	333	92
	Abnormal	29	8
	General Total	362	
	ABNORMALITIES		
	Structural chromosome abnormalities		
	Deletions		
F/1 F/13	46,XX, del(5p13) 46,XX/ del(18)(p13)		
	Total	2	0,6
	Translocations		
F/2 F/6 M/9 F/13 M/15	46,XX,t(6;11)(q25;q23) 46,XX,t(16;19)(q24.1;p11) 46,XY,t(5;12)(q34;p12) 46,XX,t(8;7)(?) 45,XY,robt(14;21)		
	Total	5	1,4
	Inversions		
F/11 M/7 M/13 M/5	46,XX,inv(14)(q13;q24) 46,XY,inv(9)(p12;q21) 46,XY,inv(9)(p12;q21) 46,XY,inv(9)(p11;q13)		
	Total	4	1,1
	isochromosome		
F/1 F/18	46,Xi(Xq) 45,X/46,Xi(Xp)		
		2	0,6
	Fragilities		
M/3 M/6 M/13	46,XY,fra (8p23),(15%) 46,XY,fra (5q24)(20%) 46,XY,fra(13q32)(17%)		
	Total	3	0,8
	General total	18	5,0
	Numerical chromosome abnormalities		
F/1 M/4 monthly F/1 monthly F/5 monthly F/4	47,XX,+21 47,XY,+21 47,XX,+21 46,XX/47,XX+21 47,XX, +mar 45,X 45,X 45,X		

F/9 F/14 F/15 F/11 F/7 F/10	45,X 45,X 45,X/46,XX(20%)		
	Total	11	**3,0**
	General total	11	**3,0**

IV. Discussion

CAs are among the common factors that adversely affect both fetal and postnatal growth. A large variety of chromosomal abnormalities are associated with GR. These CAs can affect a variety of autosomes as well as the sex chromosomes. Some of the known genetic associations of intrauterine growth restriction are placental genes, maternal and fetal genes. These genes the causes phenotypic changes, many of which are important for growth and development. In a recent study, the total incidence of cytogenetic anomalies in patients with growth retardation was reported to be 15,0% (5). In the present study, the total frequency of CAs was found at 8,0%. This ratio is important that we found. These CAs were the structural aberrations (translocations, deletions, inversions, isochromosome and fragilities) and numerical aberrations were 5,0% and 3,0%, respectively.

A large variety of CAs is associated with endocrine disorders. These CAs can affect a variety of autosomes as well as the sex chromosomes. Intrauterine growth restriction (IUGR) is defined as fetal growth less than the normal growth potential of a specific infant because of genetic or environmental factors. Genetic causes can contribute to 5-20 % of IUGR, especially for early-onset growth-restricted fetuses, and include various abnormalities, such as CAs, e.g., trisomy 21, 18, 13, and 16 (7,8). A search of the London Dysmorphology Database at http://www.hgmp.mrc.ac.uk/DHMHD/view.html identifies a series of partial chromosome deletions or duplications that are associated with short stature and pituitary abnormalities. These include the following deletions: del(4)pter-p16, del(7)q32-qter, del(13)q22-qter, del(14)q22-q23, del(18)p, del(18)q21-qter, del(22)pter-q11 and duplications: dup(1)q25-q32, dup(9)p, dup(9)pter-q22 and dup(11)q23-qter. Trisomy 16 is known to be a lethal chromosomal abnormality in the nonmosaic state; however, in the presence of placenta mosaicism, trisomy 16 can result in IUGR.

In the present study, we found a higher rate (5,0%) of structural CAs. These ratios of structural CAs were translocations (1,4%), inversions (1,1%), fragilities (0.8%), deletions (0,6%) and isochromosomes (0,6%), respectively. The translocations in all metaphases were found in 5 cases (1,4%). These translocations were found in specific regions of chromosomes t(6;11)(q25;q23); t(16;19)(q24.1;p11); t(5;12)(q34;p12); t(8;7)(?); robt(14;21) (Table 1). Phenotype-specific reciprocal translocations are the most biologically and clinically significant karyotypic changes in PGR. In the present study, the four translocations [t(6;11)(q25;q23); t(16;19)(q24.1;p11); t(5;12)(q34;p12); t(8;7)(?)], we found are new structural formations that are not found in other studies. Therefore, these structural formations may be important new findings in the development of growth retardation.

The most commonly reported manifestations of 16q deletions are severe growth and developmental disorders and anomalies of the craniofacial, visceral, and musculoskeletal systems. We found one translocation instead of adeletion at 16q. This translocation was between t(16;19)(q24.1;p11) chromosome regions in one patient. Here, the break in the 16q24.1 region, the broken part does not disappear, and adherence to the 19 chromosomes may show phenotypic effect similar to the 16q deletion. Thus, only one of these deletions, 16q22.1; q24.1, (9) encompasses our patient's deletion. While not reported in patients with an isolated 16q deletion.

Autosomal abnormalities, including the deletion of chromosomes 4 (Wolf-Hirschhorn syndrome), 5 (Cri du chat syndrome), 13, 18, and ring chromosome structural alterations, have all been associated with IUGR (8, 10). Indeed, we detected a patient with a Cri-du-chat syndrome among our patients. However, del (18)(p13) was found in our patient for the first time. Indeed, the growth hormone deficiency has been described with 18p- and 20p chromosomal deletions (11,12). Therefore, this deletion may be important new findings in the development of growth retardation.

In the present study, pericentric inversionon the chromosome 9 and paracentric inversion on the chromosome 14 were noted in 4 cases [inv(14)(q13;q24); inv(9)(p12;q21); inv(9)(p12;q21); inv(9)(p11;q13)]. Only three cases with pericentric inversion on chromosome 9 were detected. Although this finding is usually considered as a normal variation of chromosome 9. But, paracentric inversion on chromosome 14 was found in our patient for the first time. This inversion may be important new findings in the development of growth retardation.

Abnormalities of sex chromosomes, including complete deletion of X chromosome resulting in Turner's syndrome (45XO) (TS), extra or missing sex chromosomes also have been associated with IUGR. The most common features of TS are pre- and postnatal

growth retardation and gonadal dysgenesis. Although Growth hormone (GH) secretion has been reported to be normal or paradoxically increased, in most patients with gonadal dysgenesis, pituitary insufficiency has been reported in several patients. These abnormalities in GH secretion in Turner syndrome are probably secondary to the absence of sex hormones during adolescence. Girls with TS have mild growth impairment at birth, grow slowly during infancy and at the onset of childhood and have delayed onset of secondary sex characteristics as well (13). We found that 1,7% of cases had abnormal karyotype who had cytogenetic findings in favor of TS, and one of these was a mosaic form of TS. In addition to numerical abnormalities of chromosome X, two types of structural abnormality of chromosomes including isochromosome of the long and short arms of the X was found in two cases [Xi(Xq) and 45,X/46,Xi(Xp)].

Between numerical chromosomal abnormalities, the most common is Down syndrome (DS) which affect nearly 1:600 live born infants. Delayed development and behavioral problems are often reported in children with DS, and in girls with short stature and growth retardation. Affected individuals' speech and language is develop later, and may be more difficult to understand. Indeed, we found 1.1% (4 cases) DS among our patients, and one of these was a mosaic form of DS. We also found a marker chromosome in one of our patients.

We observed chromosomal fragilities in 0.8% of the patients, and these was a mosaic form. Identification of the basis of instability at FS and the related genes provides an entree to understanding the important aspects of chromosomal instability, which may be a effect that PGR cause. However, the FS is a very interesting subject for the study of clinical disorders, which can lead to the formation of deletions and translocations. At the same time, the characterization of FS has demonstrated that they are associated with genes that relate to tumorigenesis and behavioural disorders (14,15).

V. Conclusion

IUGR is an important health problem of developing countries around the world. There are multiple causes for IUGR including maternal, fetal, placental, and genetic factors. At the same time, postnatal growth also depends on cause of growth retardation, postnatal nutritional intake, and social environment. There is strong association between IUGR, chromosome aberrations and congenital malformations. We showed that a significant proportion of pediatric cases especially unexplained growth retardation had karyotypic abnormality, these are most commonly translocations, Turner syndrome and Down syndrome, respectively. We recommend cytogenetic study for such cases for early diagnosis and management. It is necessary that children with TS and DS be diagnosed as soon as possible so they may achieve the maximum benefit of growth hormone therapy.

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