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Original Articles

A Cytogenetic Survey of 8584 Children Referred for Suspected Congenital Disorders: The Experience of a Children's Hospital in China from 1996 to 2010

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Abstract

Objectives: We evaluated the type and incidence of different chromosomal abnormalities among paediatric patients presented with congenital abnormalities in a paediatric hospital over the past 15 years. ***Material and methods:*** Peripheral blood lymphocytes were obtained from 8584 paediatric patients with suspected chromosomal aberrations in the Children's Hospital of Zhejiang University School from 1996 to 2010. Their age were between 0 and 18 years. Cytogenetic analysis was performed by G-banding technique. The cases were grouped according to the reasons of referral for cytogenetic analysis. The frequency of various abnormal karyotypes was analysed. ***Results:*** The main indications for cytogenetic analysis were congenital genitourinary defect, which accounted for 39.6% (3402/8584). The referrals of congenital genitourinary defects group increased while other groups decreased during 2006-2010 compared to 1996-2000. Abnormal karyotypes were found in 24.4% (2094/8584) and 77.0% (1612/2094) had autosomal abnormalities. Among them, trisomy 21 was the most frequent one. The remaining 23.0% (482/2094) were sex chromosome abnormalities, 199 cases were structural abnormalities and 283 cases were numerical abnormalities. The ratio of autosomal abnormalities to sex chromosome abnormalities showed a decrease trend. Turner syndrome accounted for 12.7% (265/2094) of abnormal karyotypes. Eighty nine cases of XY female (46,XY complete gonadal dysgenesis) and 58 cases of XX male (46,XX testicular disorder of sexual development) were diagnosed, which consisted of 7.0% (147/2094) in all chromosomal anomalies. ***Conclusions:*** The incidence and distribution of cytogenetic abnormalities by karyotype were reviewed. The high rate of chromosomal abnormalities (24.4%) found in our referred population demonstrates the importance of cytogenetic evaluation in patients who are clinically abnormal. The main clinical indications for genetic analysis were congenital genitourinary defects, the ratio between sex chromosome abnormality and autosomal abnormality elevated with the increase of cases referral for congenital genitourinary defects. This is due to referral bias of a paediatric medical center with developed paediatric urology subspecialty. Our data may help in providing some correlation data for genetic counselling on this aspect.

Key words Abnormal karyotypes; Children; Cytogenetic testing; Disorders of sex development; Monosomy

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Introduction

Genetic factors have long been recognised to be an important cause for syndromal and nonsyndromal congenital anomalies. Previous cytogenetic investigations demonstrated that constitutional chromosomal abnormalities affect about 0.5% of live-born infants and contribute to a significant proportion of birth defects. Congenital anomalies are also one of the leading causes of neonatal morbidity and mortality in many countries.[1,2] Common chromosomal abnormalities have traditionally been diagnosed during the neonatal period by conventional cytogenetic methods such as trypsin-Giemsa staining (GTG banding) analysis.[3] Despite advances in prenatal diagnosis and perinatal management, congenital anomalies still remain a major cause of neonatal morbidity and mortality, and most of the underlying genetic causes remain unknown.

Precise diagnosis for the child's pattern of congenital anomalies is critical because it may guide the subsequent medical and surgical management as well as helping to provide accurate information to families regarding the prognosis and recurrence risks. During the last decades, study of fetal karyotypes has become a very important tool for genetic counselling on the recurrence risk and/or pregnancies at risk. Even though prenatal diagnosis is gaining popular recently, there are still some children who haven't been detected before birth. This group of patients with chromosomal abnormalities identified after birth still remain an important problem and many of their structural abnormalities requires early intervention. It is therefore necessary to provide diagnosis as soon as possible.

The Children's Hospital of Zhejiang University School of Medicine is the largest paediatric referral center of Zhejiang province, serving approximately 8 million children below the age of 18 years. The present study was aimed to investigate the frequency of different chromosomal abnormalities in patients referred for cytogenetic analyses a from 1996 to 2010. This study is the first report on this particular topic from the Southeast region of China. We hope our study can raise the awareness of clinicians (especially paediatricians) on the cytogenetic abnormalities so they can offer proper genetic counselling.

Subjects and Methods

All samples for cytogenetic analyses were analysed in the Medical Biology and Genetic Department Laboratory at the Children's Hospital of Zhejiang University School of Medicine. The informed consents were obtained from children's parent/guardian or other legally authorised representative if necessary (hereafter referred to as the legally authorised representatives). A detailed interview was conducted before cytogenetic analysis with medical history obtained. Patients presented with congenital anomalies, intellectual disability, short stature and other miscellaneous defects were included in the study. According to the reason for referral for cytogenetic study, we divided them into four groups: 1) group suspected for Down's syndrome **(Down's syndrome group),** who presented with a specific clinical stigmata (such as up slanting palpebral fissure, prominent epicantic folds, micrognathia, etc.); 2) group suspected for Turner syndrome **(Turner syndrome group)** who presented with short stature and characteristic physical phenotypes (such as low hairline, webbed neck, down slanting eyes, shield chest), primary amenorrhea, delayed puberty, absence of ovaries, etc.; 3) **congenital genitourinary defects group** (including ambiguous genitalia, abnormality of male external genitalia, concealed penis, cryptorchidism, etc); and 4) **miscellaneous group** (including intellectual disability, developmental delay, obesity, congenital heart diseases and other indications not listed in the above three group).

Sex in mammals is genetically determined and defined at the cellular level by sex chromosome complement (XY males and XX females) and defined at the phenotypic level by the development of gender-specific anatomy, physiology, and behavior. Disorders of sex development (DSD) in humans are characterised by a complete or partial mismatch between genetic sex and phenotypic sex. Combined with medical genetics, ultrasound diagnostics, hormonal profile and pathology, DSD can be diagnosed.

For routine cytogenetic analysis, 0.5-1.0 mL peripheral blood samples were collected from the patients and stored into heparinized test tubes. They were cultured in complete lymphocyte culture medium within an incubator at 37°C for 72 hours. Metaphases were harvested by adding colcemid for 60 minutes followed by hypotonic KCl treatment for 5 minutes and fixation using standard 3:1 methanol-acetic fixative (Gibco Life Technologies Ltd, UK). The karyotypes were determined by G-banding using trypsin and Giemsa (GTG) (Seabright, 1971) and C-banding using barium (Sumner, 1972) as well as Giemsa (CBG) (Salamanca and Armendares, 1974) when necessary. At least 30 cells were routinely analysed; in cases of mosaicism, this number was increased to approximately 100 metaphases. In our hospital, there isn't any change of laboratory protocol or personnel in the Genetic Department

Laboratory in the past 18 years. The karyotypic descriptions were reported according to the International System for Human Cytogenetic Nomenclature recommendations (ISCN, 1995).

The percentage of abnormal cases in each group and the distribution of the numerical and structural abnormalities were determined. The frequencies were compared to similar studies using the Z-test for comparison of two frequencies with unequal variance.

Results

There were 8584 patients less than 18 years old referred for cytogenetic analyses from 1st January 1996 to 31st December 2010. Among them, 6047 were male and 2537 were female, the ratio of male to female was 2.38:1. The number of samples gradually increased from 1996 to 2010, which were 193 cases in 1996 and increased to 1115 cases in 2010 respectively. The ratio between cases referred for cytogenetic analyses and outpatient visits also increased in the past fifteen years, which was 1:2899 (193/559569) in 1996, 1:2227 (374/832970) in 2001, 1:1686 (669/1134914) in 2006 and 1:1371 (1115/1530332) in 2010 respectively. The ratio of males to females in the cases of cytogenetic survey increased gradually from 1996 to 2010, which were 1.7:1 (122/71) in 1996, 1.9:1 (245/129) in 2001, 2.4:1 (475/194) in 2006 and 4:1 (892/223) in 2010 respectively. The ratio of cases ≤1 years versus the cases more than 1-year-old for cytogenetic analysis showed an decreasing trend too, which was 1:1.3 in 1996, 1:1.1 in 2001, 1:1.5 in 2006, and 1:2.2 in 2010.

The main clinical indications for genetic analysis were congenital genitourinary defects, which accounted for 39.6% (3402/8584) of the total cases referred for examination in the past 15 years. The next most common referrals were miscellaneous group, which accounted for 30.4% (2611/8584) (Table 1). The percentage of cases suspected for Down's syndrome and miscellaneous group decreased gradually, which was 28.5% (55/193) and 52.8% (102/193) in 1996, 26.5% (99/374) and 41.4% (155/374) in 2001, 15.7% (105/669) and 29.1% (195/669) in 2006, 10.6% (118/1115) and 20.0% (223/1115) in 2010 respectively. The percentage of cases suspected for Turner Syndrome group ranged from 4.7% in 1997 to 18.5% in 2009. The percentage of cases presented with congenital genitourinary defects increased significantly, which was 8.3% (16/193) in 1996, 22.2% (83/374) in 2001, 39.1% (262/669) in 2001 and 58.4% (651/1115) in 2010 respectively. The referrals of congenital genitourinary defects group increased while miscellaneous group and Down syndrome group decreased during 2006-2010 period compared with 1996-2000 period (Table 2).

Abnormal chromosomes were found in 24.4% (2094/8584) of the cases. The number of abnormal karyotypes showed a gradual increase, which was 70 cases in 1996, 117 cases in 2001, 167 cases in 2006 and 190 cases in 2010. However, the detected incidence of abnormal karyotype each year decreased substantially, which was 36.3% in 1996, 31.3% in 2001, 25.0% in 2006 and 15.8% in 2010 respectively. Of these abnormal karyotypes, 77.0% (1612/2094) consisted of classical autosomal abnormalities; the

Table 1 Distribution of the clinical indications for referral of cytogenetic study from 1996 to 2010

Clinical indications at the time of the referral*	**1996**	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**Total**
Down's syndrome group	55	78	48	55	88	99	96	105	118	122	105	137	133	102	118	1459
Turner syndrome group	20	13	26	31	41	37	39	53	89	105	107	64	154	208	125	1112
Congenital genitourinary defects group	16	31	40	42	39	83	124	157	215	237	262	390	520	596	651	3402
Miscellaneous group	102	150	117	129	158	155	154	158	183	206	195	226	226	240	223	2611
Total	**193**	**272**	**231**	**257**	**316**	**374**	**413**	**473**	**605**	**670**	**669**	**817**	**1033**	**1146**	**1115**	**8584**

*__Down's syndrome group included the cases__ suspected for Down's syndrome, __Turner syndrome group included all the cases__ who presented with short stature, primary amenorrhea, delayed puberty, absence of ovaries, etc. and were suspected for Turner syndrome, __congenital genitourinary defects group__ included ambiguous genitalia, abnormality of male external genitalia, concealed penis, cryptorchidism, etc, and __miscellaneous group included all the cases__ who presented intellectual disability, developmental delay, obesity, congenital heart diseases and other indications not listed in the above three groups.

remaining 23.0% (482/2094) were sex chromosome abnormalities (Table 3). The ratio of autosomal abnormalities to sex chromosome abnormalities showed a decreasing trend, which was 15.5:1 in 1996 and 2.1:1 in 2010. Compared through 5-year periods, the percentage of sex chromosome abnormalities during 2006-2010 was higher than that during the 1996-2000 period (29.3% vs. 14.4%, p=0.000) (Figure 1).

We further investigated the 1612 cases of autosomal abnormities. Down syndrome was the most frequent one (93%, 1499/2094). Of all Down syndrome cases, 1392 cases (92.9%, 1392/1499) had classical trisomy 21 and 107 cases (7.1%, 107/1499) had a translocation, mostly Robertsonian t (14;21) and t (21;21) or were mosaics. The overall sex ratio in Down syndrome increased as well (male to female: 1.82 to 1). One hundred and twelve cases (6.9%) had other types of autochrosome abnormities including trisomy 18, trisomy 13, 46,XX,r(14), 46,XY,5p, and others (Table 4).

Among 482 cases of sex chromosome abnormalities, 199 cases were structural abnormalities and 283 cases were numerical abnormalities. Turner syndrome accounted for 12.7% (265/2094) of abnormal karyotypes, of which, 113

Table 2 The ratio of different clinical indications during different period

	1996-2000 n=1269	2001-2005 n=2535	2006-2010 n=4780	$\chi 2$ (p)
Down's syndrome group	324 (25.53%)	540 (21.3%)	595 (12.45%)	133.24 (0.000)#
Turner syndrome group	131 (10.32%)	323 (12.74%)	658 (13.77%)	1.597 (0.193)
congenital genitourinarydefects group	168 (13.24%)	816 (32.19%)	2418 (50.59%)	571.483 (0.000)#
miscellaneous group	646 (50.91%)	856 (33.77%)	1109 (23.2%)	337.096 (0.000)#

The reasons of referral for cytogenetic analysis differed between the period of 2006-2010 and 1996-2000. The ratio of cases suspected Down's syndrome and miscellaneous group decreased during 2006-2010 compared to the period 1996-2000, the ratio of cases suspected turner syndrome group kept stable or unchanged, the ratio of cases presented with congenital genitourinary defects increased significantly.

#represents $p<0.05$ the referral cases during 2006-2010 vs. The referral cases during 1996-2000 for the same clinical features.

Table 3 The number of chromosome anomalies from 1996 to 2010

	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	Total
Autosomal chromosome abnormalies	66	94	52	67	91	103	106	111	121	137	121	129	168	118	128	1612
Trisomy for chromosomes 21	63	84	46	63	89	100	103	109	117	130	112	121	147	90	115	1499
Male	40	51	33	36	56	70	70	64	79	79	75	76	104	62	75	968
Female	23	33	13	27	33	30	33	45	39	51	39	45	43	38	40	531
Other autosome chromosomes anomalies	3	10	6	4	2	3	3	2	3	7	9	8	22	18	13	113
Sex chromosome anomalies	4	8	7	16	27	14	19	26	35	50	46	50	55	63	62	482
Turner syndrome	2	3	3	8	15	6	9	15	21	22	26	21	27	34	31	243
Other sex chromosome anomalies	2	5	4	8	12	8	10	11	14	28	20	29	28	29	31	239
Total	**70**	**102**	**59**	**83**	**118**	**117**	**125**	**137**	**155**	**187**	**167**	**179**	**224**	**181**	**190**	**2094**

cases had X monosomies. Of the 199 cases with structural abnormalities in sex chromosome, combined with medical genetics, clinic indications and ultrasound diagnostics, hormonal measurements and pathology, 89 cases of XY female (XY sex reversal or 46,XY complete gonadal dysgenesis) and 58 cases of XX male (XX sex reversal or 46, XX testicular DSD) were diagnosed in our cohort, which consisted of 7.0% (147/2094) in all chromosome anomalies. There were wide variations in sex chromosome trisomies (SCTs),XYY XXX /XX, r(X), and XXY accounted for 1, 9 and 28 cases respectively. Other sex chromosome trisomy karyotypes were mosaic, including 45,X/47,XXX, 45,X/47,XYY, 45,X/46,XY/47,XYY, 46,XY/47,XXY 46,XY/47,XYY 48,XYY,+21 and 48,XXY,+21. The remaining different forms of abnormal sexual karyotypes are shown in Table 5.

Discussion

1. The Detection Rate

Chromosome abnormalities are one of the main causes of congenital defects. We analysed the results of 8584 samples referred to our laboratory for cytogenetic studies

Table 4 The distribution of autosomal chromosome abnormalities

Autosomal chromosome anomalies	n	Autosomal chromosome anomalies	n	Autosomal chromosome anomalies	n	Autosomal chromosome abnormalities	n
Structure abnormalities		46,XY,t(14q21q)	27	Number abnormalities		47,XX,+20	1
46,XX,t(14q21q)	22	46,XY,t(21q21q)	22	45,X,-22,-Y, +t(22;Y)	1	46,XY/47,XY,+21	16
46,XX,t(21q21q)	9	46,XY,t(13q21q)	5	45,XX,-21	2	45,XY,-22/46,XY	1
46,XX,t(15q21q)	4	46,XY,21/21,tan	1	45,XX,-22	1	46,XY/47,XY,+8	1
46,XX,t(13q21q)	3	46,XY,-21,+r(21;21)	1	45,XY,t(13q;14q)	4	47,XY,+13	4
46,XX,2p-	2	46,XY,-13,+t(13:21)	1	45,XY,-21	1	47,XY,+21	913
46,XX,5p-	3	46,XY,r(4)	1	45,XY,t(14,15)(15p11::14q11)	1	47,XY,+22	1
46,XX,16q+	1	46,XY,r(21;21) (q2→p11::p11→q12)	1	45,XY,t(15q21q)	1	47, XY,+7q-	1
46,XX,18p-	3	46,XY,r(18)	1	45,XX, t(10q;14q) (10pter→q24::14q→13qter)	1	47,XY,+22q-	1
46,XX,18q-(pter→ q21)	1	46,XY,4q+	1	45,XY 13/13	1	47,XY,+8	1
46,XX/46,XX,3q-	1	46,XY,5p -	3	45,XY, t(15q21q)	1	47,XY,+18	3
46,XX,del(7)		46,XY,t(5p;13q)					
(pter→q11::q22→qter)	1	(5qter→5p14::13q14→13qter) (13pter→13q13)	1	45,XY,18p-	1	47,XX,+13	1
46,XX,21p+	1	46,XY,8p-	2	46,XX/47,XX,+21	14	47,XY,18q-,3q-,+t(3;18) (3qter→q22::18q22→ q21::3q13→cen)	1
46,XX,22p+	1	46,XY,13q-	2	47,XX,+18	15	48,XY,+21,+5	1
46,XX,22q+	1	46,XY,15p+	2	47,XX,+21	479	Total	1473
46, XX,r(13)	2	46,XY,18P-	2	47,XX,+18p- (pter→q12)	1		
46,XX,r(14)	4	46,XY,20q-	1	47,XX,+cen	1		
46,XX,r(18)	1	46,XY,t(14q;15q)	1	47,XX,21p+	1		
46,XX,+t(4q11q)	1	46,XY, inv(11)(q13; q22) (pter→q12::q22::q23→qter)	1	47,XX,del(5)(q15),+(5;21) (5qter→q21::21q12→pter)	1		
46,XX,t(6p-; 22q+)	1	46,XY,inv(7) (q11→p22::q11→qter)	1	47,XX,t(21; 5q) del(5)(pter→q21)	1		
46,XX der(20q)	1	**Total**	**139**				

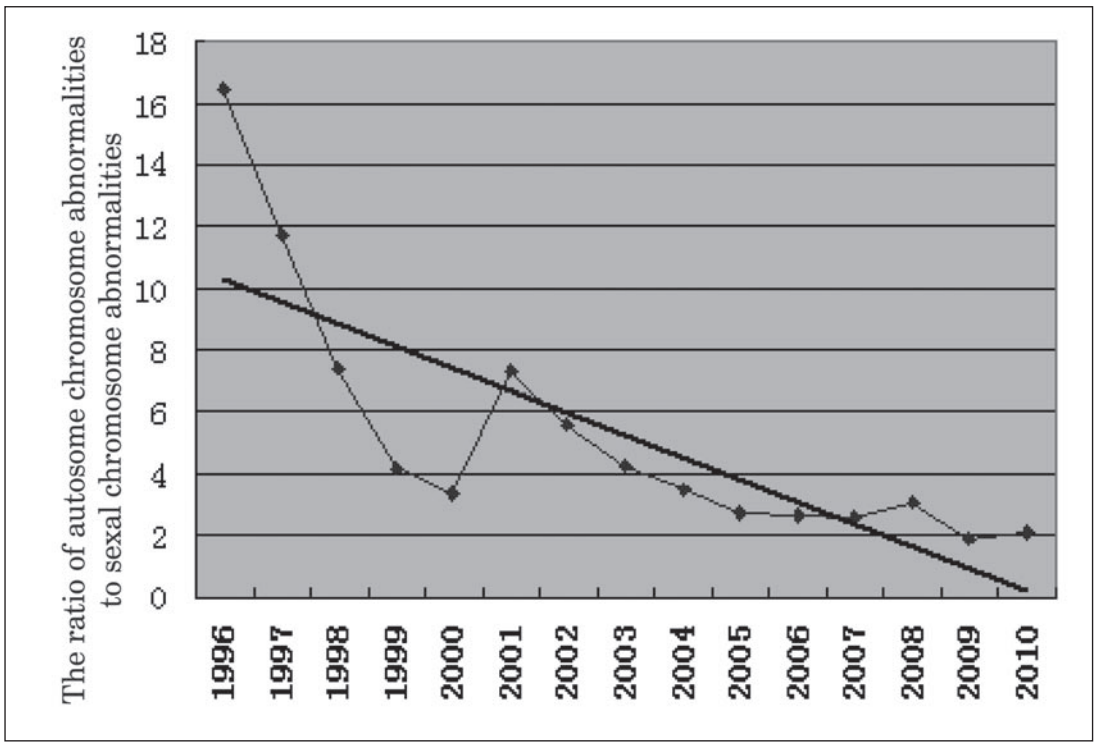

Figure 1 The ratio of sex chromosome abnormalities to autosomal chromosome abnormalities. The ratio of sex chromosome abnormalities to autosomal chromosome abnormalities showed a decreasing trend from 1996 to 2010.

Table 5 The distribution of sex chromosome abnormalities

Sex chromosome abnormalities	n	Sex chromosome abnormalities	n	Sex chromosome abnormalities	n	Sex chromosome abnormalities	n
Structure abnormalities		46,X,Yq-	5	45,X/46,X,r(X)	24	46,XY/47,XXY	1
46,Xi(Xq)	8	46,X,del(Y)(q11)	1	45,X/46Xp-	1	46,XY/47,XYY	7
46,X,Xp-	8	46,X Xq-,delq11,Xq-	1	45,X/46,X,Xq-p-	2	47,XXX	8
46,X,Xq-	16	46,X Xq11 q-(X)	1	45,X/46,Xq-	13	47,XYYdel(Y)(q1.2)	1
46,XX/46,XY	2	–		45,X/46,XX	35	47,XXY	28
46,XY(female)	89	46, X YP+ t(Y;Y)	1	45,X/46,XY	12	47,XX,r(X)	1
46,XX(male)	58	**Total**	**199**	45,X, ins(9) (pter→p12::q12→q13::p11→qter)	1	48,XYY,+21	1
46,XY/46,X dic(Y)(p11)	2	**Number abnormalities**		45,X/46,XY	12	48,XXY,+21	2
46,XYp+	4	45,X	113	45,x/47,XXX	8	48,XXXX	2
–		45,X +acc	1	45,X/47,XYY	2	49, XXXXY	1
46,X del(Y)(p11)	2	45,X/46,Xi(Xq)	18	45,X/46,XY/47,XYY	1	49,XYYYY	1
46,XY,p-	1	45,X/46,X,del(X)(p11→q12)	1	45,X/47,XX,+21	2	**Total**	**283**

from 1996 to 2010. As we know, this is one of the largest paediatric case series for cytogenetic studies in China to date.

The last decades has witnessed the significant improvement in the health status and disease profile in China. The major causes of death and disability have shifted from a predominance of nutritional deficiencies and infectious diseases to chronic non-communicable diseases. This transition occurs not only among different disease categories, but also within a specific disease category.[4] The ratio between cases referred for cytogenetic analyses and outpatient visits increased in the past fifteen years in our hospital-based study. It partly demonstrated the changes of disease profiles and case mix in our hospital, which meant more patients suspected for congenital anomalies or genetic disorders are coming to our hospital. Zhang et al analysed the karyotype of 4,046 cases aged from 1 day to 17 years old in the Children's Hospital of Fudan University during January 1990 to December 2006, there were 660 (16.3%) cases with abnormal chromosome karyotypes.[5] Li et al investigated 4628 children aged from 1 day to 18 years old in the Children s Hospital of Chongqing Medical University from January 1982 to December 2006, a total of 22.67% (1049/4628) patients were identified to have abnormalities.[6] Abnormal chromosomes were found in 24.4% (2094/8584) of our cases, The detection rate in our hospital was a little higher than the reports from other children's hospitals. However, the detection rate and chromosome malformation profiles from paediatric hospital are different from that of Chinese general population.[7] However, the number of abnormal karyotype detected annually decreased substantially from 36.3% in 1996 to 15.8% in 2010 respectively. Chromosomal analysis is applicable only for patients with a strong clinical suspicion of a specific genetic defect. This is often challenging in children with non-stereotypic or syndromal genetic disorders, because their clinical presentations may not be evident yet or may be atypical. They may also lack specific syndromic features initially and evolve only at a later age. The significant decrease of the detection rate may also be due to less stringent referral criteria because each paediatrician can request a chromosomal analysis in our hospital without restriction.

2. Clinical Indications for Referral

We aimed to estimate the correlation between the referral pattern and chromosomal abnormalities in our patients' cohort. The most common referral for cytogenetic analysis were congenital genitourinary defects in this study which accounted for 39.6% of the total cases. However, lower percentages of chromosomal anomalies (7.0%) were detected in the congenital genitourinary defects group. The abnormality rates were lower than previous reports.[1,2] On the other hand, rapid progress has been made in the urology department and led to drastic increase in referral over the recent years. In addition, the doctor in urology department may pay more attention to the genetic aetiology of congenital genitourinary defects and therefore referred more cases for karyotype analysis. Other identified problems included lack of proper phenotypic description and difficulty in obtaining familial follow-up for proper diagnosis and genetic counselling. Less specific referrals for congenital genitourinary defects group may also be related to the decrease in the female to male ratio in the referral. The profiles of congenital abnormalities referred for karyotype analysis in our paediatric hospital had a different pattern when compared to the general population with universal birth defects monitoring. Lu et al reported 316 (1.11%) birth defects in a total of 28,542 births from 2006 to 2009 and the first four leading diseases were congenital heart disease, anomaly of the locomotor system, defect in digestive system and neurocanal defect.[8] It also suggests that the clinical paediatrician may focus more in some specific congenital defects leading to a bias in referral for karyotype analysis.

3. Abnormal Karyotypes

The identification of specific types of chromosomal abnormalities in Down syndrome children is important as it provides relevant information for patient management and family counselling.[9] Among chromosomal abnormalities found in our study, 77.0% (1612/2094) consisted of autosomal anomalies. Down syndrome (1499/2094, 71.6%) is the most common type of autosomal chromosome abnormality. Turner syndrome accounted for 12.7% (265/2094) of abnormal karyotypes. This frequency were similar to those reports from other paediatric hospital. Trisomy 21 accounted for 69.4% (458/660) and Turner syndrome accounted for 15.9% (105/660) of the total chromosomal abnormalities reported by the Children's Hospital of Fudan University.[5] In the Children's Hospital of Chongqing Medical University, 874 (83.32%) cases were euchromosome malformation, of which Down syndrome was the commonest. One hundred fifty nine cases (15.16%) were sex chromosome abnormalities.[6] The highest abnormality detection rates were among the known stereotypic chromosomal syndromes.

Of all Down syndrome cases, 1392 cases (92.9%, 1392/1499) had classical trisomy 21. Classical trisomy 21 was present in 96.24% in a Moroccan population.[10] Among the 5737 cases registered in England and Wales between 1989 and 1993, 95% had classical trisomy 21. In 4% there was a translocation.[11] The profiles of Down syndrome in our hospital were similar to the previous studies. A strong trend towards an association between the cosmic ray activity level and the incidence of Down syndrome had been reported in Israel.[12] A well designed questionnaire including clinical and laboratory data collected prospectively is necessary for studying of the etiology and phenotypic consequences of Down syndrome. Though regional sample may not represent the characteristic of the general population in terms of the prevalence of specific congenital anomalies, this study may provide useful information in phenotype correlation with cytogenetic profiles.

4. Sex Chromosome Anomalies

DSDs occur in at least 1 in 100 live births and include relatively mild forms such as hypospadias (1 in 500 births) as well as more severe conditions such as ambiguous genitalia (1 in 4,500 births) and complete sex reversal (46, XY females and 46, XX males; 1 in 20,000 births).[13,14] The majorities of sex chromosome abnormalities are never diagnosed or are diagnosed later in life. Sex chromosomal abnormalities were found 17.6% among the chromosomal abnormalities in Southeast Turkey.[15] Twenty three percent were sex chromosome abnormalities in our cohort, which was a little higher than above reports. In this data, the most common sex chromosome abnormality was Turner syndrome (12.7%, 265/2094) followed by complete sex reversal (46,XY females and 46,XX males), which accounted for 7.0% (147/2094). There is a wide variation between our data and previous reports in sex chromosome anomalies,[15] which may be related to differences in referral pattern. According to data from the European Surveillance of Congenital Anomalies (EUROCAT) database on sex chromosome trisomies (SCT) cases, the prevalence of SCT was 1.88 per 10,000 births. Prevalence of XXX, XXY and XYY were 0.54, 1.04 and 0.30 per 10,000 births respectively.[16-17] The SCT incidences in this study are lower than those published, most probably due to a later registration (over 14 years of age of the child) of these diagnoses. Although the aetiology of DSD is not known, some cases of complete XX male and XY female sex reversal are associated with translocations or mutations of sex-determining region Y (SRY).[18] Submicroscopic genomic rearrangements may be the cause in a significant proportion of DSD. Microdeletion methods such as fluorescence in situ hybridization (FISH) may improve the diagnosis of DSD.

5. Double Aneuploidies (DAs)

The chance of two chromosome abnormalities or double aneuplodies (DAs) is very small. This probably was caused by strong intrauterine and postnatal selection against such double aneuplodies. Collectively, we identified one case of nonmosaic 48,XXY,+21; one case of 48,XYY,+21; and one case of 48,XY,+21,+5 in our cohort, which were less than expected and reported.[19] The nonrandomness of such DA events was considered to be evidence that nondisjunction (NDJ) may be genetically determined, Mechanisms may include greater accessibility of disomic ovum to Y-carrying sperm, promotion of NDJ in ovum by Y-bearing sperm and maternal age-related factors.

Limitations of this study include that patients with congenital defects were not characterised on the basis of their congenital defects due to limited clinical information available. In addition, the data are derived from a single clinical service and therefore cannot represent the general population. Thirdly, the unavailability of chromosomal microarray analysis (CMA) or microarray-based comparative genomic hybridization (aCGH) may lead to the under-detection of some cryptic cytogenetic conditions like chromosome 22q11.2 deletion, Prader-Willi syndrome and SRY microdeletion in the present survey.[20] Array CGH or CMA will increase the detection rate and enable the clinical diagnosis of chromosomal abnormalities at a much higher resolution.

In conclusion, this is one of the largest cohorts of cytogenetic testing in paediatric population from a single paediatric medical center. The high rate of chromosomal abnormalities (24.4%) found in our referred population demonstrates the importance of cytogenetic evaluation in patients who are clinically abnormal. The main clinical indications for genetic analysis were congenital genitourinary defects. The ratio between sex chromosome abnormality and autosomal chromosomal abnormality showed an increasing trend with the increase of referral for congenital genitourinary defects in the recent years. This study provides useful information for clinical genetic counselling.

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