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Cytogenetic Study of Malaysian Neonates with Congenital Abnormalities in Maternity Hospital Kuala Lumpur

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Summary

During the period 1 January 1990 – 31 December 1990, 68 neonates with congenital abnormalities were successfully analysed for chromosome abnormalities in order to determine the contribution of chromosome aberrations to the aetiology of congenital abnormalities. The neonates were karyotyped employing the G-banding technique. Twenty-nine babies showed abnormal chromosome karyotypes. Twenty-six were observed to have classic trisomy syndromes; ie. trisomy 21 (32.3%), trisomy 18 (3.0%), and trisomy 13 (3.0%). The mean maternal age of the mothers with babies having normal karyotype was lower than the mean maternal age of the mothers having babies with abnormal karyotypes. From this study the incidence of congenital abnormalities due to chromosomal abnormalities is found to be 1:838 livebirths. Frequency of newborns having abnormal chromosomes is 0.14% for Malays, 0.12% for Chinese and 0.06% for Indians.

Key Words: Chromosomal aberrations, Congenital abnormalities, Chromosomal abnormalities

Introduction

There is a very high mortality among human conceptuses before, during, and shortly after birth and chromosome abnormalities are among the most important causes. At least 7.5% of these pregnancies have chromosome disorders, but the majority are aborted spontaneously, thus the frequency of chromosomal disorder at birth is 0.6%[1]. Individuals who have abnormal chromosome complements fall into two categories: i) those who have an abnormal number of chromosomes and ii) those who have abnormality of chromosome structure. Numerical abnormalities such as aneuploids, are usually the result of new mutations, such as due to non-disjunction, and is rarely passed on to the offspring. Structural rearrangements arise as a result of breakage and abnormal rejoining with or between chromosomes, and a majority of these are transmitted from parent to offspring. The presence of chromosomal aberrations may cause congenital abnormalities. Studies conducted in several developed countries[2,3] have shown that genetic factors, especially chromosome abnormality is one of the causes of congenital disorders among the

newborns. Thus correct diagnosis is very important for management of patients. Genetic counselling on the recurrent risk of the abnormalities can be undertaken by the physicians and appropriate management given. This study was conducted to determine the types and prevalence of congenital abnormalities due to abnormal chromosomes, and to correlate the cytogenetic findings with clinical features.

Materials and Methods

The study included selected neonates with congenital abnormalities which have been delivered in Maternity Hospital Kuala Lumpur (MHKL) and referred to Special Care Nursery, MHKL during the period from 1st January 1990 until 31st December 1990. The criteria for the patients' selection were:

i) neonates with unexplained congenital anomalies
ii) neonates with dysmorphic syndromes of unknown aetiology
iii) neonates with short stature and developmental delay
iv) neonates suspected of having chromosomal disorders

These neonates were of one to 28 days-old when referred to us. About 2 – 3 ml venous blood were taken from the neonates and were collected in heparinised tubes. Blood was cultured for 3 days and harvested using the standard cytogenetic techniques with a little modification[4]. Trypsin-Giemsa banding was used for routine chromosome identification[5] while C-banding[6] was only performed when heteromorphisms were suspected. Thirty metaphase spreads were screened, 8 were photographed and 1 to 2 were karyotyped before a diagnosis was made. In the presence of mosaicism, 100 cells were observed or all slides screened.

Results

Of the 81 blood cultures taken only 68 were successfully harvested and karyotyped. Four neonates that were referred for ambiguous genitalia were diagnosed as male genotypically. Thirty-nine neonates had normal chromosome complement, and 29 (42.6%) had abnormal karyotypes. Of the 29 neonates with abnormal karyotypes, 26 were observed to be trisomic, 2 had translocation, t (21;21) and one had abnormal chromosome 5 (Table I).

15 of the 39 (38.5%) male neonates (including those with ambiguous genitalia) had abnormal chromosome. Amongst the 29 female neonates, 14 (48.3%) had

Table I
Cytogenetic findings in neonates using G-banding
(1st January 1990 – 31st December 1990)

Karyotype	Total	Percentage
Normal		
1. 46, XY	19	
2. 46, XX	16	
Total	35	51.4
Trisomy		
1. 47, XX(Y), +21		
a. XY, + 21	13	
b. XX, + 21	9	
Total	22	32.3
2. 47, XX(Y), +18		
a. XY, +18	–	
b. XX, +18	2	
Total	2	3.0
3. 47, XX(Y), +13		
a. XY, +13	1	
b. XX, +13	1	
Total	2	3.0
Structurally abnormal chromosome		
1. 46, XY, t (21; 21)	1	
2. 46, XX, t (21; 21)	1	
3. 46, XX, 5p+	1	
Total	3	4.4
Ambiguous genitalia		
1. 46, XY	4	
2. 46, XX	0	
Total	4	5.9
Total	68	100.0

abnormal chromosome. Twenty-six of the 29 neonates that had abnormal karyotypes had classic trisomies, that is, trisomy 21 (75.9%), trisomy 18 (6.9%) and trisomy 13 (6.9%). Overall, 35.3% of the neonates had Down syndrome. Down syndrome was observed in 36.8% male and 33.3% female neonates.

Of the 28 neonates referred for Down syndrome, 24 (85.7%) was confirmed to be so. Twenty-two of these neonates (91.7%) had trisomy 21 and 2 (8.3%) had Robertsonian translocation, t (21;21). Mosaicism was not detected in this study. Three neonates were referred for Edward syndrome, but only 2 (66.7%) were confirmed to be positive. For neonates with unspecific congenital abnormality, 2 of the 30 (6.7%) had abnormal karyotype. Table II shows the result of the chromosomal analysis based on clinical findings.

Among the three major ethnic groups, 20 of the 40 Malay neonates (50%) had chromosome abnormalities. Chromosome abnormality was detected in 11 of the 23 (47.8%) males and 9 of the 11 (52.9%) females. Among the Chinese neonates, 6 of the 16 (37.5%) seen had abnormal chromosome. Three of the 10 males, and 3 of the 6 females had abnormal chromosomes. Two of the 8 Indian neonates (25%) had abnormal chromosomes. One of the 5 (20%) males and 1 of the 3 females (33.3%) had abnormal chromosome complement. Table III shows the distribution of chromosome abnormality according to ethnicity and sex. Down syndrome was detected in 10 male and 8 female Malay newborns, in 3 male and 1 female Chinese newborns and 1 male and 1 female Indian newborns (Table IV).

Table II
Cytogenetic findings in neonates according to clinical findings

Clinical Findings	Total			Karyotype				Grand Total	Rate of Detection (%)
				Normal		Abnormal			
	Male	Female	Total	Male	Female	Male	Female		
Having clinical features of Down's Syndrome	17	11	28	3	1	14	10	28	85.7
Cleft lip and palate	1	2	3	1	1	0	1	3	33.3
Having clinical features of Edward's Syndrome	1	2	3	1	–	–	2	3	66.7
Short web neck low set ears, nipples widely spaced*	3	5	8	3	4	–	1	8	12.5
Micropenis and/or hypertrophy of labia majora*	3	–	3	3	–	–	–	3	–
Microcephaly	2	0	2	2	0	–	–	2	–
Dysmorphic	7	10	17	6	10	1	–	17	5.9
Ambiguous genitalia	4	–	4	4	–	–	–	4	–
Total	38	30	68	23	16	15	14	68	

* *Categorised as unspecific congenital abnormality*

Table III
Numbers of babies having chromosome abnormalities according to ethnicity and sex

Ethnic group	Total babies		Chromosome abnormality		Abnormalities %	
	Male	Female	Male	Female	Male	Female
Malay	23	17	11	9	47.8	52.9
Chinese	10	6	3	3	30.0	50.0
Indian	5	3	1	1	20.0	33.3
Others	1	3	–	1	–	33.3
Total	39	29	15	14	38.5	48.3

Table IV
Number of babies having Down Syndrome according to ethnicity and sex

Ethnic group	Total babies		Chromosome abnormality		Abnormalities %	
	Male	Female	Male	Female	Male	Female
Malay	23	17	10	8	43.4	47.1
Chinese	10	6	3	1	30.0	16.7
Indian	5	3	1	1	20.0	33.3
Others	1	3	–	–	–	–
Total	39	29	14	10	35.9	34.5

During the study period, Maternity Hospital Kuala Lumpur had 24,295 deliveries. Eighty-one neonates with congenital abnormality were referred to us and 29 of the 68 successfully karyotyped chromosomes had abnormal chromosomes. Based on this result, the incidence of chromosomal abnormality among the liveborns is 1:838 (1.20 per 1000 livebirths). Twenty-four neonates had Down syndrome, thus the incidence of this syndrome among the livebirths was 1:1012. Two neonates each were observed to have trisomy 13 and 18.

Among the Malays, 0.14% neonates showed chromosomal abnormality. Down syndrome was seen in 0.12% Malay neonates. Six of the 4,092 (0.15%) Chinese neonates had chromosome abnormalities and Down syndrome was seen in 0.10%. Amongst the Indian neonates, 0.06% had chromosomal abnormalities which was entirely due to trisomy 21. Table V shows the incidence of chromosome abnormalities according to ethnicity.

Discussion

Of the 24,295 babies delivered alive in Maternity Hospital Kuala Lumpur, only 68 out of 81 referred cases were karyotyped. The incidence of chromosome abnormalities is calculated as 1.20 per 1000 livebirths. This value may well be an underestimate of the true incidence owing to failure in culturing 13 samples. The incidence is low compared to other similar studies[7,8,9,10]. Our study only focussed on the babies with congenital abnormalities. Some diseases have their symptoms expressed at a later stage, thus there is a possibility

that some newborns were excluded from the study sample. Jones[11], estimated that only 1/3 of babies with abnormal karyotypes had distinctly abnormal phenotypes. The incidence of chromosomal abnormalities in general population is 0.5 – 1%[12].

Our study showed no significant difference in the incidence of chromosomal abnormalities among the males and females, that is, 1:831 and 1:832 respectively ($p<0.05$). There was also no significant difference among the various ethnic groups ($p<0.05$).

Table V
Incidence of Down Syndrome in Maternity Hospital according to ethnicity
(1st January 1990 – 31st December 1990)

Ethnic group	Number of babies with abnormal karyotype	Total livebirths	Incidence per 1000 live-births	Ratio
Malay	18	14,687	1.226	1:816
Chinese	4	4,092	0.733	1:1364
Indian	2	3,541	0.565	1:1771
Others	0	1,975	–	–
Total	24	24,295	0.988	1:1012

Autosomal trisomies are the most frequent chromosome aberration seen. Jacob *et al*[8] found that the incidence rate was 1.7 per 1000 livebirths. In our study, 38.2% neonates had autosomal trisomy giving an incidence rate of 1.07 per 1000 livebirths.

Amongst the trisomies, trisomy 21 represents the major aberration in this study. Of the 26 autosomal trisomies seen, 22 were trisomy 21 (84.6%). It had been reported that about 1/2 of babies with autosomal trisomies were trisomy 21[13].

The incidence of Down syndrome in our study is 0.988 per 1000 livebirths (1:1012). This finding is lower than reported in similar local studies by Boo *et al*[14] and Goh & Yeo[15]. However, the result of our study still falls within the range seen in other countries; that is 0.32 – 3.4 per 1000 livebirths[16,17]. Hoe *et al*[18] observed that Down syndrome was more prominent in female babies, however our study showed no significant difference ($p<0.05$). Frossman[19] on the other hand, reported that males have higher frequency.

Trisomy 21 is always been associated with non-disjunction originated from the mothers. Maternal age plays an important role in non-disjunction. In our study, mothers having trisomic babies were observed to be older than mothers having babies with normal karyotype; 34 ± 2.53 years and 29 ± 0.14 years respectively ($0.01 > p > 0.001$) (Table VI). The mean maternal age of mothers having Down's syndrome child was observed to be 33.7 ± 2.81 years. Mothers with

Table VI
Age of mothers of the babies referred for cytogenetic analysis
(1st January 1990 – 31st December 1990)

Constituent	Mothers' age (years)							Total
	15–19	20–24	25–29	30–34	35–39	40–44	N.A.*	
Normal chromosome**	2	6	9	7	5	2	8	39
Ordinary trisomy	–	2	2	5	8	3	6	26
Structurally abnormal	–	1	2	–	–	–	–	3
Total	2	9	13	12	13	5	14	68

N.A Information not available*
*** Including babies with ambiguous genitalia (four males)*

advanced maternal age especially those above 35 years have a higher risk in getting a trisomy 21 child (t-distribution, t = 3.40, at 0.01 significant level). Boo *et al*[14], in their study at the same hospital, also observed that the incidence of Down syndrome increased with maternal age. These findings were supported by earlier studies[20,21]. The risk of a mother having a Down syndrome child is 1 in 2,000 at 20-34 years, and the risk increases exponentially with age[22]. Boo *et al*[14] observed that the risk of getting a Down syndrome child was higher in Malays compared to Chinese and Indians. Our study did not exhibit any significant difference in risk ($p<0.05$). The incidence of other trisomies; that is Edward's and Patau's syndrome is low; 1:12,072 and 1:12,148) respectively. Goh & Yeo[15] reported a higher incidence in the local population. Borovik *et al*[23] also reported a low incidence in his study; 1:24,397.

The other type of abnormalities seen in our study were translocation and recombinant chromosome. The translocation observed was Robertsonian translocation involving the G-group, t (21;21). In one of the babies, we observed that her chromosome 5 had an additional segment on the p-arm. Family study showed that she inherited the abnormal chromosome from her mother.

In conclusion, the contribution of chromosome aberration to the aetiology of congenital abnormality is significant. It serves to stress the importance of a chromosomal analysis in any neonate with congenital abnormalities so that appropriate management can be given at an early stage. In every case where an abnormality is observed, it is very important to determine if this is inherited from either parent, as the implication for genetic counselling is tremendous.

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