CLUSTERING OF TRISOMY 18 IN KUWAIT: GENETIC PREDISPOSITION OR ENVIRONMENTAL?

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Background: This study describes 59 newborns with regular trisomy 18 (Edwards' syndrome, T18) who were ascertained clinically and cytogenetically at the Kuwait Medical Genetic Centre from 1994 to 1997, out of 118 T18 cases identified from 1980 to 1997.

Materials and Methods: T18 cases were ascertained clinically and cytogenetically shortly after birth. In addition to assessing the T18 birth prevalence rate and confidence limits during the years 1994-1997, we investigated the possible etiological factors by a case-control study with normal healthy newborns. Studied factors included gender, parental age, birth order, abortion, clinical variables (presentation, amniotic fluid and mode of delivery), and survival.

Results: The average T18 birth prevalence rate during the period was 8.95 per 10,000 live births (95% confidence limits 6.66-11.23). The T18 cases were mostly females, with a male:female ratio of 1:2.1, and the majority (53%) died before the second week of life. Maternal age above 30 years was found to be a significant factor for T18.

Conclusion: This high T18 birth prevalence rate suggests clustering of T18 in the highly inbred population of Kuwait. Such clustering may indicate a possible environmental, and to a lesser extent, genetic predisposition to aneuploidy nondisjunction.

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Key Words: Clustering, trisomy 18, nondisjunction, polymorphism.

Since the first description of trisomy 18 (Edwards' syndrome, T18) by Edwards et al. in 1960,[1] many aspects of the syndrome have been reported, including birth prevalence, phenotype, parental age and clustering with other syndromes.[2-11] The aim of this study is to describe T18 clustering in Kuwait, and present possible etiological factors.

Materials and Methods

During the period (1980-1997), 118 cases with T18 were ascertained clinically and cytogenetically at the Kuwait Medical Genetic Centre. Of these, 59 T18 cases were delivered during the period 1994-1997. The ascertainment was performed shortly after birth. A case-control study was undertaken which included 131 normal healthy newborns randomly selected from newborns delivered during the same month of the corresponding T18 cases. No attempts were made to match T18 cases and controls on basic characteristics (e.g., gender, birth order, parental age, etc.), in order to be able to study these variables in cases and controls.

Chromosomal studies were carried out using peripheral blood following the Hungerford technique,[12] and the Seabright technique for trypsin G banding.[13] A minimum of 20 cells were scored and 5 cells were karyotyped. If mosaicism was detected, 50-100 cells were scored. The cytogenetic findings were interpreted according to ISCN.[14] Parents were investigated in case of structural rearrangements, recurrent aneuploidy or other chromosomes. Other relevant investigations included

TABLE 1. *Birth prevalence rates and confidence limits of trisomy 18 (T18) cases during 1994-1997 in Kuwait.*

Year	Live births	T18	Birth prevalence rate/ 10,000 live births	95% CI
1994	14,848	16	10.78	5.50, 16.06
1995	16,100	17	10.56	5.54, 15.58
1996	18,009	11	6.11	2.50, 9.72
1997	16,996	15	8.83	4.36, 13.29
Total	65,953	59	8.95	6.66, 11.23

CI=confidence interval.

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Data were collected on a specially designed format, including information about gender, maternal age, paternal age, birth order, reproductive history (abortion, presentation, amniotic fluid and mode of delivery), and survival. The data were processed using the Statistical Package for Social Sciences (SPSS),[15] applying a cut-off level for significance at $P \leq 0.05$. The 95% confidence interval for the T18 birth prevalence rate was calculated using the Poisson approximation,[16] because of the small number of cases compared to the number of live births. The chi-square test for linear trend[17] was used to test the linear trend in T18 birth prevalence rates.

Results

The average overall T18 birth prevalence rate during the period (1994-1997) was 8.95 per 10,000 live births (95% confidence limits 6.66-11.23) (Table 1). There was a linear trend in the T18 birth prevalence rates, however, it was not significant due to the increased rate in 1997 (chi-square=0.949, P=0.330). All cases were due to regular T18, with no evidence of mosaicism among patients or their parents. Only a single family with T18 in sibs and another patient with double aneuploidy 48,XX, +18, +21, were found.

Table 2 exhibits characteristics of T18 cases and controls. There was a preponderance of females among T18 cases, with a male:female ratio of 1:2.1. The distribution of maternal age showed that 30.5% of the T18 mothers were 35 years old and above, compared to 10.7% in the control group. The difference was statistically significant, P=0.002. The mean maternal age ($\pm$SD) in the T18 patient and control groups was 31.9 ($\pm$7.3) and 27.1 ($\pm$5.2) years, respectively (P<0.001). The paternal age of 42.4% of the T18 cases was 45 years and above, compared to 33.5% in controls, the difference of which was not statistically significant.

Concerning abortion, 14.6% of T18 mothers experienced two or more abortions, compared to 11.4% in controls—the difference was not significant. With respect to clinical variables, abnormal presentation (mainly breech) occurred in 12.7% of the T18 mothers' group, compared to 5.4% in the control group (P<0.05). Mode of delivery was not spontaneous in 43.2% of T18 cases (90% of them were delivered by cesarean section), compared to 15.3% in controls (P<0.001). Polyhydramnios was recorded in 9.3% of T18 cases, compared to 1.5% in the control group (P<0.001) (Table 2). Fifty-three percent of the 118 T18 cases died before the second week of life, 29.4% died before the third week, 11.8% died before the end of the second month, and 5.8% died after the third month. Only one T18 case is still surviving after the age of seven months.

TABLE 2. *Characteristics of 118 trisomy 18 patients and 131 normal controls.*

Variable	Patients (%)	Controls (%)
Gender		
Male	38 (32.2)	63 (48.1)
Female	80 (67.8)	68 (51.9)
Maternal age (yr)		
<30	66 (55.9)	92 (70.2)
30-34	16 (13.6)	25 (19.1)
35-39	27 (22.9)	10 (7.6)
40-44	7 (5.9)	4 (3.1)
≥45	2 (1.7)	0
Paternal age (yr)		
<30	55 (46.6)	56 (42.7)
30-34	13 (11.0)	31 (23.7)
35-39	21 (17.8)	26 (19.8)
40-44	10 (8.5)	6 (4.6)
45-49	10 (8.5)	5 (3.8)
50-54	6 (5.1)	5 (3.8)
≥55	3 (2.5)	2 (1.5)
Birth order		
1	34 (28.8)	25 (19.1)
2	17 (14.4)	32 (24.4)
3	16 (13.6)	19 (14.5)
4	16 (13.6)	25 (19.1)
5+	35 (29.9)	30 (22.9)
Abortion		
0	89 (75.4)	86 (65.6)
1	12 (10.2)	30 (22.9)
2	15 (12.7)	9 (6.9)
3	2 (1.7)	4 (3.1)
4	0	2 (1.5)
Presentation*		
Normal	101 (85.6)	124 (94.7)
Abnormal	15 (12.7)	7 (5.4)
Amniotic fluid**		
Decreased	2 (1.7)	1 (0.8)
Average	102 (86.4)	128 (97.7)
Increased	11 (9.3)	2 (1.5)
Mode of delivery		
Spontaneous	67 (56.8)	111 (84.7)
Cesarean	46 (39.0)	16 (12.2)
Forceps	1 (0.8)	0
Vacuum	0	1 (0.8)
Abnormal	4 (3.4)	3 (2.3)

*Two were missing in the T18 group; **three were missing in the T18 group.

Discussion

Trisomy 18 is a well-known autosomal chromosomal disorder, giving rise to a well-defined clinical syndrome.[1] It originates, as a rule, from nondisjunction during maternal or paternal germ cell development.[6] Eighty percent of T18 cases involve full trisomy, the majority of whom are females, with a median survival time of less than three months. Double aneuploidy, structural aberration and mosaicism involving chromosome 18 have also been recorded.[18]

The birth prevalence rate of Edwards' syndrome varies considerably, from 1:3000 to 1:11,000 live births.[2,3,7,19-24] In the present study, the T18 average birth prevalence rate was 8.95 per 10,000 live births, which is significantly higher than the previous rate reported from Kuwait during

1984-1985 (1.1 per 10,000) and in 1986 (4.61 per 10,000).[25] Although clustering of births of children with Edwards' syndrome has been previously reported, no studies reported such a high rate.[10,26] Clustering of Down syndrome in time and space has been reported.[5,10,27,28] On the other hand, the association of clustering of Edwards' syndrome with an increased birth prevalence rate of infants with Down syndrome has been noted in the literature.[10] This finding was also noticed in the Kuwait Maternity Hospital, where the birth prevalence of Down syndrome children delivered during 1986 was 2.1 per 1000 live births,[25] and a higher birth prevalence rate of Down syndrome was recently ascertained (4 per 1000 live births). These results indicate that the two autosomal chromosomal aberrations are related to the same etiological events. In addition, the birth prevalence of T13 cases also increased during the same period.

Variation in the birth prevalence of nondisjunction which may lead to clustering is still unknown. However, it seems reasonable to assume that exogenous factors could be partially responsible. Such variations in findings in different parts of the world indicate that some of the etiological factors of nondisjunction of T18 are of environmental nature.[4] The possibility of environmental pollution hazards due to the use of heavyweight oil products may be raised as an exogenous factor. Alternatively, increased birth prevalence rate of different aneuploidy, together with the change in the nature and rate of some malformations delivered in Kuwait, may raise the question of environmental hazards precipitated by the Gulf War in the region, and hence support the hypothesis of environmental exogenous factors.

On the other hand, genetically mediated susceptibility or predisposition to nondisjunction may exist in man. Since the postulation of an autosomal recessive gene causing nondisjunction,[29] some authors have attempted to reveal the genetic role in nondisjunction.[30-36] The precise nature of this genetic role has not yet been established. Besides, it has been proposed that chromosomal polymorphism of constitutive heterochromatin may predispose to nondisjunction in man.[4]

Lastly, the high birth prevalence rate of T18 in the present study may be partially attributed to cultural and religious factors. These factors prohibit the termination of prenatally identified malformed T18 babies and other anomalies, and hinder the availability of prenatal diagnostic procedures which are the only effective preventive measures. However, the limitation of benefitting from prenatal diagnosis cannot be solely blamed for such a high birth prevalence T18 rate.

In conclusion, there has been an increase in birth prevalence of deliveries of T18 cases in Kuwait since the Gulf War in 1990-1991. This clustering of the T18 cases may be associated with environmental, genetic and cultural factors. The infrequent and inconsistent references in the literature dealing with chromosomal clusters in different parts of the world, as well as in Kuwait, seem to incriminate environmental rather than genetic factors.

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