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Trisomy 18 in Kuwait

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Background Trisomy 18 (Edwards' syndrome, T18) is the second most common trisomy in man. We describe 118 children with regular T18 who were ascertained clinically and cytogenetically in the Kuwait Medical Genetics Centre during 1980–1997.

Methods Ascertainment of T18 cases was performed shortly after birth. Chromosomal studies were carried out in addition to other relevant investigations. To investigate the factors associated with TI8, a case-control study was carried out with 131 normal healthy newborns. Studied factors included maternal and paternal age, birth order, abortion, associated malformation, and survival. Multiple logistic regression analysis was used to adjust for confounding between variables.

Results There was a preponderance of females among T18 cases (female:male ratio 2.1:1). The majority of T18 cases (53%) died before the second week of life. The most common associated anomalies were: congenital heart (38.1%) and gastrointestinal (25.4%). Multiplicity of malformations was also observed. Significant seasonal variation in T18 cases was detected with a peak in spring. Of the 118 T18 cases, 59 were delivered during 1994–1997 (average overall T18 birth prevalence rate 8.95 per 10 000 live births [95% CI : 6.66–11.23]). Concerning maternal age, 30.5% of the T18 cases' mothers were ⩾35 years compared to 10.7% in the control group. The difference was statistically significant, $P = 0.002$. Logistic regression analysis showed that maternal age >30 years was a significant risk factor for T18, after adjusting for confounding with paternal age. Paternal age and abortion were not found to be significant risk factors.

Conclusion Trisomy 18 birth prevalence rate is high in Kuwait with advanced maternal age as a significant risk factor.

Keywords Trisomy 18, maternal age, Kuwait

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Trisomy 18 (Edwards' syndrome, T18) is the second most common trisomy in man. It occurs in approximately 1:3000 live births.[1,2] It is manifested by characteristic external features as well as life threatening abnormalities. Many of these abnormalities require surgical correction during the neonatal period.[3] Since the first description of T18 by Edwards *et al.* in 1960,[4] many aspects of the syndrome have been reported in the literature including birth prevalence, phenotypes, parental age, seasonal variation, and clustering with other syndromes.[5–14] The aim of this paper is to describe T18 in Kuwait, and present some associated factors.

Methods

During 1980–1997 118 infants with T18 syndrome were ascertained clinically and cytogenetically in the Kuwait Medical Genetic Centre which was established in 1979. It provides comprehensive genetic services to all areas of Kuwait. This includes antenatal and premarital counselling with emphasis on primary infertility, repeated pregnancy loss, congenital malformations, chromosomal disorders, mental retardation, congenital heart and vision disorders, short stature and genetic blood disorders. Karyotyping is not performed for abortuses or stillbirths. Indications for liveborn infants being karyotyped by the Centre are malformations or other problems observed at birth. The ascertainment is performed shortly after birth. All the 118 children with T18 syndrome were liveborn to residents in Kuwait. Chromosomal studies were carried out using peripheral blood following the Hungerford technique,[15] and the Seabright technique for Trypsin G banding.[16] A minimum of 20 cells were examined in each patient, increased to 100 cells if mosaicism was suspected. The cytogenetic findings were interpreted according to the International System for Human Cytogenetics (ISCN).[17]

Other relevant individual investigations included biochemical, haematological and skeletal surveys, echocardiography, ECG, hormonal study and CT head. Parents were

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investigated in case of structural rearrangements or recurrent aneuploidy of other chromosomes.

In order to study the factors associated with T18, a group-matched case-control study was undertaken which included 131 normal newborn controls who were randomly selected from newborns delivered during the same month in which T18 cases were identified. Excess controls (about 10% more than cases) were selected to guard against incomplete data and missing information.

Statistical methods

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), consanguinity, survival and associated anomalies. The data were processed using SPSS,[18] applying a cutoff level for significance of $P \leqslant 0.05$. The χ^2 for linear trend[19] was used to test the trend in birth prevalence rates. The 95% CI for a birth prevalence rate was calculated using the Poisson approximation[20] because of the small number of cases compared to the live births. The z-normal test was used to assess the significance of the difference between two proportions. The student t-test was used to compare between means of two quantitative variables.

We used an approximation of χ^2 based on periodic regression[21,22] to determine seasonal variation of T18 cases. The year is taken as 360 degrees and the midpoint of each month of the year is assigned an angular value, t, for January (15 degrees) through December (345 degrees). Multiple regression analysis was then performed between the number of monthly T18 cases as the dependent variable, sin(t) and cos(t) as independent variables. The resulting sum of squares due to regression divided by the monthly average of T18 cases results in a statistic which approximately distributed as χ^2 with 2 degrees of freedom.

The Mantel-Haenszel procedure was used to calculate odds ratios (OR) and their 95% CI using EPI.[19] The multiple logistic regression analysis was used to adjust for confounding between variables. The dependent variable was binary (0 for control, 1 for T18 case), while the independent variables were maternal age, paternal age and abortion. The adjusted OR for risk factors were computed as the exponents of the coefficients of the logistic regression.

Results

There was a preponderance of females among T18 cases (female:male ratio 2.1:1). 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 1 compares other characteristics of 118 T18 patients and 131 controls.

Table 1 Characteristics of 118 trisomy 18 patients and 131 normal controls, Kuwait

Variable	Patients n (%)	Controls n (%)
Maternal age (years)		
<30	66 (55.9)	92 (70.2)
30–	16 (13.6)	25 (19.1)
35–	27 (22.9)	10 (7.6)
40–	7 (5.9)	4 (3.1)
45+	2 (1.7)	0 (0.0)
Paternal age (years)		
<30	55 (46.6)	56 (42.7)
30–	13 (11.0)	31 (23.7)
35–	21 (17.8)	26 (19.8)
40–	10 (8.5)	6 (4.6)
45–	10 (8.5)	5 (3.8)
50–	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 (0.0)	2 (1.5)
Presentation[a]		
Normal	101 (85.6)	124 (94.7)
Abnormal	15 (12.7)	7 (5.4)
Amniotic fluid[b]		
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)
Caesarean	46 (39.0)	16 (12.2)
Forceps	1 (0.8)	0 (0.0)
Vacuum	0 (0.0)	1 (0.8)
Abnormal	4 (3.4)	3 (2.3)

[a] Two missing were in the T18 group.

[b] Three missing were in the T18 group.

Maternal age

The distribution of maternal age showed that 30.5% of the T18 cases' mothers were ⩾35 years old, compared to 10.7% in the control group. The difference was statistically significant, $P = 0.002$. The mean maternal age (±SD) in the T18 patient and control groups were 31.9(±7.3) and 27.1(±5.2) years respectively, $P < 0.001$. The OR for maternal age ⩾35 years, with reference to maternal age <35 years, was 3.67 (95% CI : 1.78–7.67), (Table 2). To adjust for confounding between maternal and paternal age, logistic regression analysis was used and showed that as maternal age increases to 30 years, the adjusted OR increases to 2.035 relative to the baseline category <30 years; OR increases to 9.900 at age 35; 13.009 at age ⩾40 (Table 3). The wide range of the last OR may be attributed to the small numbers of mothers aged ⩾40 in the case and control groups.

Paternal age

The paternal age of 42.4% of T18 cases was ⩾45 years, compared to 33.5% in controls but the difference was not

Table 2 Odds ratio and 95% CI of maternal age, paternal age and abortion in a case-control study of 118 trisomy 18 patients and 131 controls, Kuwait

	T18 cases	Controls	Odds ratio	95% CI[a]	*P*-value
Maternal age (years)					
⩾35	36	14	3.67	(1.78–7.67)	<0.001
<35	82	117			
Paternal age (years)					
⩾45	19	12	1.90	(0.83–4.41)	0.098
<45	99	119			
Abortion					
Yes (⩾2 abortions)	17	15	1.31	(0.59–2.94)	0.471
No (0/1 abortion)	100	116			

[a] CI = confidence interval.

Table 3 Logistic regression analysis for maternal age, paternal age and abortion in a case-control study of 118 trisomy 18 patients and 131 controls, Kuwait

	Odds ratio (adjusted)	95% CI	*P*-value
Maternal age (years)			
<30	1.000		
30–	2.035	(0.762–5.436)	0.157
35–	9.900	(2.740–35.762)	0.0005
40+	13.009	(1.867–90.630)	0.010
Paternal age (years)			
<30	1.000		
30–	0.458	(0.199–1.055)	0.067
35–	0.387	(0.130–1.153)	0.088
40–	0.378	(0.080–1.789)	0.219
45–	0.505	(0.103–2.475)	0.399
50+	0.172	(0.022–1.367)	0.096
Abortion			
No (0/1 abortion)	1.000		
Yes (⩾2 abortions)	1.086	(0.494–2.386)	0.837

statistically significant. The OR for paternal age ⩾45 was 1.90 (95% CI : 0.83–4.41) (Table 2). To fix the confounding between paternal and maternal age, we used the logistic regression analysis which showed that as paternal age increases, the adjusted OR (risk for T18 syndrome) does not significantly change. This confirms that development of T18 syndrome is not significantly related to paternal age (Table 3).

Abortion

Concerning abortion, 14.6% of T18 cases' mothers experienced two or more abortions, compared to 11.4% in controls but the difference was not significant. The OR was 1.31 (95% CI : 0.59–2.94) (Table 2). The logistic regression analysis showed that the OR for ⩾2 abortions with reference to (0/1) abortion is 1.086 which is not statistically significant as a risk for T18.

Consanguinity

We were not able to study consanguinity since it was unknown in 35 T18 cases. However, among the known consanguinity cases, the frequency of consanguinity in cases was similar to that in the control group.

Clinical variables

With respect to clinical variables, abnormal presentations (mostly breech) occurred in 12.7% of T18 mothers, compared to 5.4% in the control group, $P < 0.05$. Mode of delivery was not spontaneous in 43.2% of T18 cases; 90% were delivered by caesarean 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 1).

Malformations

With regard to malformations, Table 4 depicts the most common malformations which were found associated with T18 patients: congenital heart (38.1%), gastrointestinal (25.4%) and limb (24.6%) abnormalities and microcephaly/hydrocephalus (20.3%). Table 5 shows multiplicity of malformations: 24.6% had a single malformation, and a similar proportion had two malformations; 17.8% had three malformations, and 9.3% had four malformations.

Survival of T18 cases

Of the 118 T18 cases, 53% died before the second week of life, 29.4% died before the third week, 11.8% died before the end of

Table 4 Types and frequency of the associated anomalies detected among 118 trisomy 18 cases, Kuwait

Anomalies	Frequency	Percentage
Congenital heart		
Ventricular septal defect, patent ductus arteriosis, pulmonary valve dysplasia	45	(38.1)
Gastrointestinal		
duodenal atresia, imperforated anus, diaphragmatic hernia, oesophageal atresia, gastro-oesphageal fistula	30	(25.4)
Limb		
polydactyly, arthrogryposis, absent fibula, radial aplasia, deformed hands	29	(24.6)
Head		
microcephaly, hydrocephalus, trigonocephaly	24	(20.3)
Eye		
microphthalmia, synchia of eye lids, cloudy cornea	13	(11.0)
Omphalocele	13	(11.0)
Genital		
hypospadia, absent scrotum, undescended testis	11	(9.3)

Table 5 Multiplicity of malformations in 118 trisomy 18 cases, Kuwait

Multiplicity of malformations	Frequency	%
Single	29	(24.6)
Two	29	(24.6)
Three	21	(17.8)
Four	11	(9.3)
None	28	(23.7)

Table 6 Birth prevalence rates and 95% CI of trisomy 18 cases, 1994–1997, Kuwait

Year	Live births	Trisomy 18	Birth prevalence rate per 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)

Table 7 Seasonal distribution of 59 trisomy 18 (T18) cases ascertained 1994–1997, Kuwait

Season	Fall (Sept–Nov)	Winter (Dec–Feb)	Spring (Mar–May)	Summer (Jun–Aug)
T18 cases	15	10	24	10

the second month, and 5.8% died after the third month. Only one T18 case is still surviving after the age of 7 months.

Analysis of the T18 cases during the last 4 years (1994–1997)

In order to highlight the magnitude of the T18 syndrome in Kuwait, we selected the last 4 years. Table 6 exhibits the birth prevalence rates of T18 cases per 10 000 live births, and their 95% CI. The average overall T18 rate was 8.95 per 10 000 live births (95% CI : 6.66–11.23). There was a linear trend towards decrease in the T18 rates, however it was not significant due to the increased rate in 1997 (χ^2 for linear trend = 0.949, $P = 0.330$). There was significant seasonal variation of T18 patients with a peak in spring ($\chi^2 = 8.04$, $P < 0.05$) (Table 7).

Discussion

Trisomy 18 is a well-known autosomal, chromosomal disorder giving rise to a well-defined clinical syndrome.[4] It originates as a rule from non-disjunction during maternal or paternal germ cell development.[9] Eighty per cent of Edwards' syndrome cases had the full trisomy; the majority were females with a median survival time of less than 3 months. Double aneuploidy, structural aberration and mosaicism involving chromosome 18 were also recorded. Trisomy 18 presents with characteristic external features as well as life threatening abnormalities.[2] The most prevailing clinical features noted in over 75% of the T18 cases included developmental retardation with failure to thrive, poor sucking, hypotonia followed by hypertonia, limited adduction, flexion deformities, overlapping of fingers, hypoplastic nails, short sternum and various other congenital anomalies.[23,24] Trisomy 18 mosaicism with mild phenotype was also recorded.[25]

The birth prevalence rate of Edwards' syndrome varies considerably from 1:3000 to 1:11 000 live births.[1,5,6,10,12,26–29] In the present study, the T18 average annual birth prevalence rate was 8.95 per 10 000 live births which is significantly higher than a previous rate reported from the same population during the period 1984–1985 (1.1 per 10 000) and in 1986 (4.61 per 10 000).[13,30] Variation in birth prevalence rates of T18 in different parts of the world indicate that some of the aetiological factors of non-disjunction of chromosome 18 are environmental.[7] Trisomy 18 affects girls more than boys.[31–33] This is in agreement with our study which showed female predominance.

On the other hand, the present study showed significant seasonal variation with a peak in the spring (March–May). This finding accords with another study where six out of seven cases with T18 were born during the months of February–April.[7] Consistent with our study, the significant increase in maternal age has been shown by other authors.[7,34]

Abnormal mode of delivery is one of the characteristic features of T18. About half the T18 babies for whom data on delivery have been published were delivered by caesarean section.[28,35] Fetal distress was a factor in half of them and was the only reason for one-third of caesarean section deliveries. These findings accord with our result that the mode of delivery in 43.2% of T18 cases was abnormal (90% were delivered by caesarean section).

Concerning survival, more than 90% of T18 children die within the first year of life, few pass their first year and very few live until their teens and twenties.[1,36,37] Two studies[38,39] had reported the survival of T18 girls for more than 10 years. Root and Carey[40] studied survival in T18 patients and reported that the median survival time was 4 days and that 45% survived one week or more; they also reported 6-month survival in 9% and one-year survival in 5% of T18 patients. These results agree with survival status of T18 cases in Kuwait.

Congenital malformations are useful tools for the diagnosis of T18 in the first days of life. Intrauterine growth retardation, craniofacial and skeletal dysmorphology, congenital heart mainly ventricular septal defect (VSD) and extremity malformations are common in T18 newborns.[41–46] Hepatoblastoma have also been reported,[43,46–48] as has the CHARGE association.[49] Similarly, the following congenital malformations were recorded in our study: cardiac, gastrointestinal, limb, craniofacial, eye and genital anomalies. In the meantime, most of the T18 patients (51.7%) had two malformations or more. Other uncommon anomalies were hypoplasia of optic nerves, juxtapapillary coloboma, retinal dysplasia, neural tube defects, ventral wall defects, unilateral atypical ectrodactyly and glomerulocystic disease. These abnormalities may be caused by the abnormal expression of developmentally important genes on chromosome 18. Over-expression of the candidate gene Transthyretin (TTR) on chromosome 18 has been described for both T18 patients' liver and intestine at 20–23 weeks gestation.[1] Transthyretin transports both thyroxin and retinol and is, therefore, important for normal fetal development.

The variations in the birth prevalence of T18 from one population to another suggest that there are some environmental factors among the aetiological factors of non-disjunction of chromosome 18. The possibility of environmental population hazards due to the use of heavyweight oil products may be raised as an exogenous factor. Alternatively, increased birth prevalence of different aneuploidy together with the change in the nature and birth prevalence of some malformations delivered in Kuwait, may raise the question of environmental hazards precipitated by the Gulf war and hence support the hypothesis of environmental exogenous factors. Genetic differences between populations are another possible source

of variation in the frequency of non-disjunction. Genetically mediated predisposition to non-disjunction has been postulated in humans and other mammals,[50–56] however, its precise nature has not yet been established. It has been postulated that an autosomal recessive gene causes non-disjunction,[57] or that chromosomal polymorphism of constitutive heterochromatin is a predisposing factor in humans.[7]

In conclusion, T18 is the second most common trisomy in man and presents with characteristic features as well as life threatening abnormalities; many of them require surgical correction during the neonatal period. Children with T18 have very short life expectancy and all long-term survivors have severe mental retardation. Difficult medical and ethical issues arise over whether or not to resuscitate a newborn infant with T18. Trisomy 18 birth prevalence is high in Kuwait with advanced maternal age, polyhydramnios, abnormal presentation and mode of delivery as associated risk factors.

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