BIOCHEMICAL AND GENETIC VARIABLES ASSOCIATED WITH MOTHERS OF G_1-TRISOMY AFFECTED CHILDREN *

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The significant differences in biochemical and chromosomal characteristics, and familial history observed between group of mothers who gave birth to children affected with G_1-trisomy (Down's syndrome) and their age-matched controls, indicate that these three maternal variables, in addition to the well known variable of maternal age, are associated with etiology of the aneuploidy. Since attempts to find statistical correlation between these chromosomal and biochemical variables failed, it is believed that these three are unrelated, but very possible etiological factors.

The following report is a review of a twelve-year study involving 50 mothers with a trisomy-21 offspring and 50 age-matched healthy controls with normal children. Many biological and biochemical variables were investigated in these two groups which included PBI, antistreptolysin-0, antinuclear antibody determinations (Zsako and Kaplan 1966 and 1968, Pollard et al. 1970), and a number of them showed statistically significant results. Three of the many variables tested had significance levels of < 0.001. In addition to trisomy-21 these three were mental retardation occurring in the immediate family, the presence of an extra precipitant line in the globulin region on the immunoelectrophoretic patterns in serum of mothers with an affected child, and the chromosome association studies concerning D and G chromosomes of mothers with an affected child.

METHODS

Detailed family histories were obtained from each of the 50 mothers of the affected children, the 50 fathers of the affected children, the 50 female and 50 male control parents. All individuals were interviewed separately at least twice. Classification of a positive family history is based on occurrence of one or more individuals affected with the pathological category involved in any of the following genetic kinship: The interviewee's other children, the interviewee's parents and siblings, grandparents, grandchildren, nieces, aunts, uncles, nephews and full first cousins (Zsako and Kaplan 1968).

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The method of immunoelectrophoretic studies has been described in detail (Kerkay et al. 1971). The study was conducted with Gelman electrophoretic apparatus using the method of Grabar and Williams (1953) as modified by Scheidegger (1955). A special Agar-Noble was used with the Gelman high resolution veronal buffer, ionic strenght 0.125, conductivity 3.0 mho, pH 8.9. The electrophoresis was conducted using 300 volts for two hours at room temperature.

The method used for the study of the association of acrocentric chromosomes is again described in detail (Cotton et al. 1973). The chromosome association was studied in cultured leukocytes following the method of Moorhead et al. (1960). The slides were treated with methanol acetic fixatives and stained with carbofuchsin. The criteria used for association of acrocentric chromosomes were previously described by Cohen and Shaw (1967): an association occurs when two or more of the acrocentric chromosomes are oriented towards a common point by the satellited ends and the distance between the satellited ends of the chromosome is no grater than the long arm of a group G chromosome in the particular cell under investigation.

RESULTS

Mental Retardation. Table 1 shows that from the 50 mothers of affected children, 16 had a positive history for mental retardation in the family. From the 50 age-matched controls, only 2 mothers had a positive history for having mental retardation in the family. The statistical expression between the two groups is at the level of a chance probability of < 0.001.

From the 50 mothers of affected children, the immuno-electrophoretic study was performed on 48. From these 48 mothers, 24 showed a strong precipitant line in the globulin region; from the 48 control mothers, none showed a strong line (Table 1).

In the study of chromosome associations, the D/G ratio based on all the associations differed significantly between the two groups of mothers. The study was performed on 24 mothers of affected children and on 23 of age-matched healthy controls. The D/G ratio was under 1.5 in cells of 20 of the 24 affected mothers and in cells of only 8 of the age-matched 23 controls (Table 1).

TABLE 1

DISTRIBUTION OF MOTHERS OF G_1-TRISOMY AFFECTED CHILDREN AND CONTROLS ACCORDING TO THREE VARIABLES

Variable	Mothers of G_1-trisomy affected children			Age-matched control mothers		
	N	+	—	N	+	—
Mental retardation in family	50	16	34	50	2	48
Strong immunoelectrophoretic precipitant line	48	24	24	48	0	48
Acrocentric chromosome association ratio, D/G less than 1.5	24	20	4	23	8	15

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DISCUSSION

We wish to restrict the discussion to the group of 22 mothers of affected children and on the 22 age-matched healthy controls, because only on these groups of 22 were all three studies performed. Table 2 shows that from the 22 mothers of affected children, 21 showed a positve result on at least one of the previously described three variables. Only 1 mother of an affected child was negative and she belonged to the 45-55 age group (M-37). As one can see from Table 3, in the control group of 22, only 9 were positive for one of the variables and 13 remained negative.

Dividing the total number of 22 mothers examined in each of the two groups into their age groups, in the group between 25 and 35 years of age there were 6 mothers of affected children and 6 control mothers. All 6 of the mothers of affected children were positive for at least one variable, while in the control group only 3 out of 6 were positive. In the age group of 35-45, there were 9 mothers in each of the two groups. All 9 of the mothers of affected children were positive for at least one variable and in the control group there were 4 mothers positive and 5 negative. In the age group of 45-55, there were 7 mothers in each of the two groups. Six of the 7 mothers of affected children were positive for at least one variable, while in the control group only 2 of the mothers were positive and 5 negative.

Table 4 shows the relationship between the mothers of affected children and control mo-

TABLE 2

AGE DISTRIBUTION OF MOTHERS OF G_1-TRISOMY AFFECTED CHILDREN FOR THE THREE VARIABLES (N = 22)

Mother's age when first tested	*Code*	Mental retardation in family	Strong immunoelectrophoretic precipitant line	Acrocentric chromosome association ratio, D/G less than 1.5
Age 25-34	M-11		+	+
(N = 6)	M-27		+	
	M-39		+	+
	M-47			+
	M-48	+	+	+
	M-50		+	+
Age 35-44	M-6	+		+
(N = 9)	M-14			+
	M-19		+	+
	M-22	+	+	+
	M-30	+		+
	M-31		+	+
	M-49	+		
	M-52		+	+
	M-54			+
Age 45-54	M-2			+
(N = 7)	M-4	+		
	M-8			+
	M-32		+	+
	M-36			+
	M-37			
	M-41	+		+

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TABLE 3

AGE DISTRIBUTION OF CONTROL MOTHERS FOR THE THREE VARIABLES (N = 22)

Mother's age when first tested	*Code*	Mental retardation in family	Strong immunoelectrophoretic precipitant line	Acrocentric chromosome association ratio, D/G less than 1.5
Age 25-34 (N = 6)	C-6			+
	C-11			+
	C-20			
	C-22	+		+
	C-33			
	C-40			
Age 35-44 (N = 9)	C-3			
	C-8			+
	C-10			+
	C-18			+
	C-21			
	C-28			
	C-39			
	C-44	+		
	C-46			
Age 45-54 (N = 7)	C-2			+
	C-13			
	C-17			
	C-26			
	C-29			
	C-35			
	C-41			+

TABLE 4

DISTRIBUTION OF MOTHERS OF G_1-TRISOMY AFFECTED CHILDREN AND CONTROLS FOR A RESPONSE TO ALL THREE VARIABLES*

	Group age	N	Positive for all 3 variables	Positive for any 2 variables	Positive for only 1 variable	Negative for all 3 variables
Mothers of affected children	25-35	6	1	3	2	0
	35-45	9	1	5	3	0
	45-55	7	0	2	4	1
Total			2/22	10/22	9/22	1/22
Control mothers	25-35	6	0	1	2	3
	35-45	9	0	0	4	5
	45-55	7	0	0	2	5
Total			0/22	1/22	8/22	13/22

* Variables examined include mental retardation in the immediate family, strong immunoelectrophoretic precipitant line, and acrocentric chromosome association ratio of D/G less than 1.5.

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thers when one examines these groups for the frequency of the occurrence of the three variables; namely, mental retardation in the immediate family, strong immunoelectrophoretic precipitant line, and acrocentric chromosome association ratio. In the age group of 25-35, 2 mothers of affected children were positive for all three variables, 3 mothers for two, and 2 for one variable. None of the 6 mothers of affected children were negative for all three parameters. In the age-matched control group there were no mothers positive for all three, only 1 mother was positive for two and 2 mothers were positive for a single variable, while 3 control mothers were negative for all three tests. In the 35-45 age group 1 mother of an affected child was positive for all three, 5 were positive for two, and 3 were positive for one variable, while none of the mothers were negative for all three parameters. In this age group of control mothers none were positive for all three, none were positive for two, and 4 were positive for only one variable, but 5 control mothers were negative to all three tests. In the 45-55 age group none of the mothers of affected children were positive for all three, 2 were positive for two, and 4 were positive for a single variable, while 1 mother was negative to all three parameters. This was the only instance of a negative response to our battery of tests where none of the three variables would have alerted the physician to a potentially high-risk mother. However, advanced maternal age should have been an indicator for the possibility of this mother to give birth to a trisomy-21 child. In the age-matched control group none of the mothers were positive for all three, none were positive for two, and only 2 were positive for a single variable, while 5 mothers were negative for all three tests.

Attempts to find statistical correlation between the three biological variables failed. Therefore we believe that all three are unrelated, but possible etiological factors.

CONCLUSION

The statistically significant level of < 0.001 tends to support the idea that the above mentioned three biological variables are useful in the early detection of high-risk mothers so far as trisomy-21 offsprings are concerned. The advanced maternal age as a special factor has long been recognized (Oster 1956). We wish to advocate for the younger group of mothers who wish genetic counseling to be tested for the above described three biological variables.

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RIASSUNTO

Variabili Biochimiche e Genetiche in Madri di Bambini Affetti da Trisomia G_1

Le significative differenze in caratteristiche biochimiche e cromosomiche e nelle anamnesi familiari riscontrate fra madri di bambini affetti da trisomia G_1 (sindrome di Down) e un gruppo di controllo, indicano che queste tre variabili materne (oltre alla ben nota variabile dell'età materna) sono associate all'eziologia dell'aneuploidia. Essendo falliti i tentativi di trovare una correlazione statistica fra queste variabili cromosomiche e biochimiche, si ritiene che si possa trattare di fattori eziologici non collegati.

RÉSUMÉ

Variables Biochimiques et Génétiques chez des Mères d'Enfants Atteints de Trisomie G_1

Les différences significatives remarquées vis à vis de quelques caractéristiques biochimiques et chromosomiques, ainsi que dans l'histoire familiale, entre mères d'enfants atteints de trisomie G_1 (syndrome de Down) et contrôles, indiquent que ces trois variables maternelles (en plus de la variable de l'âge maternel) sont associées à l'étiologie de l'aneuploïdie. Ces variables chromosomiques et biochimiques ne paraissant pas corrélées, il est possible qu'il s'agisse de trois facteurs étiologiques non associés.

ZUSAMMENFASSUNG

Biochemische und Erbvariablen bei den Muttern von Kindern mit G_1-Trisomie

Einige biochemische und Chromosomenmerkmale sowie die Familienanamnese weisen erhebliche Unterschiede auf bei den Müttern von Kindern mit G_1-Trisomie (Downsches Syndrom) und bei einer Kontrollgruppe. Diese Unterschiede sprechen dafür, dass diese drei mütterlichen Variablen (Abgesehen von der bekannten Variablen des Alters der Muttter) mit der Aetiologie der Aneuploidie in Verbindung stehen. Nachdem die Versuche, eine statistische Korrelation zwischen diesen Chromosomen- und biochemischen Variablen zu finden, fehlschlugen, nimmt man an, dass es sich um voneinander unabhängige ätiologische Faktoren handelt.

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