Genealogic Study in Down Syndrome

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Abstract:

Genealogies of 66 child with trisomy 21 (Down Syndrome) as diagnosed by chromosome analysis were constructed. The control group included 198 child (three controls for each patient) with no apparent genetic pathology matched in age and sex with the patients. Genealogies of the controls were also constructed, the frequency of consanguineous marriages and average breeding coefficient in parents and grandparents of patients and controls were determined. Parental consanguinity and inbreeding coefficient showed non significant increase in patients than in control. Significant increase in the frequency of consanguinity and in inbreeding coefficient was found only in maternal grand parents of Down patients. Positive family history of Down syndrome in the relatives of the mother's patient was found. The results may suggest that consanguinity has some association with the occurrence of Down syndrome. Homozygosity of autosomal recessive gene may prevent the loss of the trisomic fetus. In addition, the results strengthen the suggestion that homozygosity for autosomal recessive gene may be a predisposing factor to meiotic nondisjunction in mothers who are the offspring of consanguineous parents.

Introduction:

Down syndrome is one of the most common human chromosomal disorders. It has an incidence of about 1 in 700 livebirths [(1)]. Its frequency at conception is much greater than that at birth, where there is evidence of increased loss of trisomy 21 conceptions with advancing maternal age [(2)].

Inbreeding or consanguineous marriages has an effect on the rates of reproductive loss, congenital malformation and genetic diseases, mainly autosomal recessive [(3)]. The association between consanguinity and genetic defects is well demonstrated in previous studies performed on well known autosomal recessive disorders among Egyptian patients such as hearing loss[(4)] and phenylketonuria [(5)].

Alfi et al (1980)[(6)] have suggested that nondisjunction in man is under genetic control in highly inbred population. This has been evidenced by the increased occurrence of Down syndrome among consanguineous parents than among non-consanguineous parents as a result of an autosomal recessive gene controlling the process of nondisjunction of chromosome 21. This hypothesis is still disputed by several studies (7-10). All these studies did not find a higher rate of consanguineous marriages among parents of Down syndrome than among control.

In Egypt, consanguinity is a common social phenomenon. It is high when compared with other populations [(11)]. So this study was conducted to investigate whether consanguinity has an effect on the genesis of meiotic or early zygotic nondisjunction.

Subjects and Methods:

The study was conducted on sixty six Down syndrome patients (31 males and 35 females). They were referred to the Department of Human Genetics, Medical Research Institute, Alexandria University during the period June 1994 - June 1997. Their age ranged from ten days to two years. The patients were diagnosed by chromosome analysis [(12)] All the cases were of the free trisomic type. Other types of karyotype were not included in the study. Genealogies of the patients were constructed to know information about consanguineous relation among the patient's parents and grandparents (both maternal and paternal). Family history of other Down syndrome individuals was recorded. A control group was randomly drawn from the population without genetic pathology. Genealogies of three control individuals for each Down syndrome patient matched on the basis of sex and age were constructed. Three controls rather than one were used to eliminate a random sporadic high variation in the data.

The effect of consanguinity expressed as the average inbreeding coefficient, was estimated[(13)]. The

obtained data was statistically evaluated using X^2 and Z tests of significance.

Results:

Table I shows the distribution of Down syndrome cases and controls according to the consanguinity of their parents. The frequency of parental consanguinity among Down syndrome children amounted to 27.3% compared to 19.7% among parents of controls. This increased consanguinity was statistically nonsignificant (X^2 = 1.26 , P> 0.05). The highest frequency in parental consanguinity was that of first cousin marriages, 19.7% for cases and 14.7% for controls. Also the difference was not statistically significant (X^2 = 0.75 , P> 0.05).

The average inbreeding coefficient was 1.3 fold increased in parents of the Down syndrome cases (0.013) than in the parents of controls (0.01003). This increase was not statistically significant (Z = 1.98 , P> 0.01).

Table II shows the distribution of the cases and controls according to their grand-parents' consanguinity. The frequency of consanguineous marriages among maternal grandparents of Down syndrome cases was too high, 16.7 % when compared to the corresponding value for controls 2%. The difference was highly significant (X^2 = 17.18 , P <0.001). The average inbreeding coefficient was also much higher in Down syndrome (0.0094) compared to (0.0013) in controls . This increase was statistically significant (Z = 4.45, P < 0.001) The frequency of consanguineous marriages in paternal grandparents of Down syndrome patients (16.7 %) was slightly higher than that in the control (14.1 %).

The difference was not statistically significant (X^2 = 0.25, P> 0.05). Also the average inbreeding coefficient for paternal grandparents of Down patients compared to that of control was not significant (Z = 1.76 , P> 0.05).

Pedigree analysis showed that two Down patients had relatives with Down syndrome. One patient had two maternal first cousins with Down syndrome (two sibs) their parents also consanguineous. In the family of the other Down patient the first cousin of her mother had Down syndrome child.

Table I: Distribution of Down syndrome (DS) cases and controls according to parental consangunity.

Consanguinity	DS		Control	
	No.	%	No.	%
Consanguineous				
1st cousins	13	19.7	29	14.7
1st cousins once removed	1	1.5	2	1.0
2nd cousins	-	-	8	4.0
3rd cousins	4	6.1	-	-
Total consanguineous	18	27.3	39	19.7
Non consanguineous	48	72.7	159	80.3
Grand total	66	100	198	100

Table II: Distribution of Down syndrome (DS) cases and controls according to their grand-parents' consanguinity.

Consanguinity	Grandparents							
	Maternal				Paternal			
	DS		Control		DS		Control	
	No.	%	No.	%	No.	%	No.	%
Consanguineous								
1st cousins	10	15.2	4	2	10	15.2	20	10.1
1st cousins once removed	-	-	-	-	-	-	8	4
3rd cousins	1	1.5	-	-	1	1.5	-	-
Total consanguin.	11	16.7	4	2	11	16.7	28	14.1
Non consanguineous	55	83.3	194	98	55	83.3	170	85.9
Grand total	66	100	198	100	66	100	198	100

Table III: Average inbreeding coefficients in parents and grand-parents of DS cases and controls.

	DS	Control
Parents	0.013	0.01003
Maternal grand parents	0.0094	0.0013
Paternal grand parents	0.0094	0.0075

Discussion:

Inbreeding is an important phenomenon genetically as it brings about an increase in homozygous genotypes and a decrease in the corresponding heterozygous forms[14].

The present results showed an increase in the parental consanguinity and in the average inbreeding coefficent of the Down syndrome children as compared to the control group . However this increase was not statistically significant these results are comparable to other studies [15,16]. These studies suggested that homozygosity at a certain locus may prevent the loss of trisomy 21 fetus.

Alfi et al[6] proposed two possible explanations for the significant increased consanguinity among parents of Down syndrome.The first explanation is that a recessive gene in the homozygous state results in mitotic nondisjunction in the Down zygote. This explanation can be excluded in the present study . Results of other study [17] support this proposal. They found a significant increase in consanguineous marriages in parents of trisomy 21 and the average inbreeding coefficient was three times greater than in the control. All these reports suggest that consanguinity should be considered as another risk factor for nondisjunction of chromosome 21 and it is independent of maternal age.

As regards grandparents, the present study revealed highly significant increase in the frequency of consanguineous marriages and in the average inbreeding coefficient in maternal (but not paternal) grand parents of Down syndrome than in control. These results support the second possible explanation of Alfi et al [6] that an autosomal recessive gene, when present in the homozygous state, in one of the parents of the trisomy 21 children predispose to meiotic nondisjunction.

Consanguineous parents have a higher probability of being themselves the offspring of consanguineous marriages. Accordingly trisomic Down syndrome may be the result of a high probability for the parents (mothers in the present study), rather than for the Down patient, to be the homozygous for the recessive gene.

More over the presence of positive family history of Down syndrome on the maternal side, in addition to the presence of increased consanguinity in the parents of Down syndrome patients and the grandparents, highly support the presence of a homozygous recessive gene which predispose to nondisjunction in the present study. Genetic predisposition to nondisjunction[18] and the suggestion of homozygosity for autosomal recessive gene as a predisposing factor to meiotic nondisjunction [19] were previously reported.

In conclusion, consanguinity was suggested to have some association with the occurrence of Down syndrome. Also it was suggested to be one of the predisposing factors to meiotic nondisjuction during oogenesis in mothers whose parents were consanguineous.

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