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Mental Retardation and Consanguinity in a Selected Region of the Israeli Arab Community

Research Article

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Abstract: The prevalence of genetic diseases and congenital malformation in the Israeli Arab community is relatively high, but its distribution is not uniform. The aim of this study was to estimate the frequency of mental retardation disorders in children living in 5 Israeli Arab villages and determine its association with consanguinity. Mental retardation was found to affect 300 children in the screened population, yielding an overall prevalence of 14.5 per 1000. Most of those affected (68%) were the offspring of consanguineous marriages. One village with a high prevalence (4.3%) of neurological hereditary diseases was studied in detail. The prevalence of neurological hereditary diseases and mental retardation associated with consanguinity in these children highlights the need to implement appropriate preventive program.

Keywords: *Mental Retardation • Consanguinity • Hereditary diseases*

1. Introduction

Hereditary diseases, especially autosomal recessive diseases, are rare in the general population. However, they become unusually frequent in certain communities worldwide as a result of genetic isolation due to social, geographic or religious factors. When a new mutation is inserted in such a population it spreads rapidly, leading to an increased prevalence of carriers and a large number of affected homozygous individuals. Consanguinity has been recognized as the main social factor leading to a high prevalence of genetic and congenital disorders [1]. Consanguinity is particularly common in Arab communities worldwide [2,3]. In the Arab community in Israel it is a major problem and contributes to the high number and prevalence of genetic diseases, congenital malformations, and neonatal mortality [4,5]. In selected Arab communities in Israel, consanguinity was recently found to have decreased [6], but its rate is still high compared to western communities. Some genetic diseases are frequent throughout the Israeli Arab population while other disorders are confined to specific geographical regions or limited to a single village, tribe, or tribal family [7].

Mental retardation (MR) is a relatively frequent condition and has a major impact on the lives of the affected individuals, their families, and society. MR is defined as a disability characterized by remarkably low intellectual functioning (IQ < 70) in conjunction with significant limitations in adaptive functioning [8]. The estimated prevalence of MR is 1% to 3% of the general population [9]. Clinical etiologies of congenital

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MR are diverse and include chromosomal anomalies, recognizable malformation syndromes, monogenic syndromes, structural brain abnormalities, and environmental factors. Mentally retarded individuals without major physical abnormalities or neurological abnormalities are diagnosed as having non-syndromic mental retardation (NSMR). Clinical observations, as well as studies of large families with MR in males have highlighted the importance of genes located on the X chromosome. The collective efforts of many research scientists have led to the identification of 59 genes associated with syndromic and non-syndromic X-linked MR [10]. The X-linked MR may account for approximately 15% to 25% of mentally retarded males [11]. In contrast, only two autosomal genes have been shown to cause autosomal recessive NSMR [12]. However, more than 50% of individuals with MR remain undiagnosed [13]. One gene locus for NSMR was identified in an Israeli Arab village, where the carrier frequency was found to be 1 in 11 newborns [14]. Another gene locus was recently identified as a cause of autosomal recessive NSMR in one large Turkish consanguineous family [15].

The present study was undertaken to determine the prevalence of MR and its association with parental consanguinity in a selected portion of the Israeli Arab community. Investigation of MR-spectrum disorders is vital for improving health care. This can be achieved by identifying and diagnosing their molecular genetic basis, with a view to developing preventative programs aimed at reducing the occurrence of these inherited genetic disorders.

2. Material and Methods

2.1. Study Population

We investigated five Arab villages in the northern part of Israel. The five villages (denoted A, B, C, D, and K for ethical considerations) have populations of: 7,729, 12,107, 13,172, 9,119, and 9,315 respectively. The study group comprised the full pediatric population (0–18 years) in each village, numbering: 2,711, 4,810, 5,000, 4,200, and 4,166 children, respectively. Many families in these villages, like most of the Muslim population of Israel, favor consanguineous marriages, mostly between first cousins [6]. Village K, which was founded 300 years ago, was studied in detail because of the high frequency of MR-spectrum disorders.

2.2. Data Collection

Data on health care and families histories during the years 2005 and 2006 were collected from the files of health care clinics in each village. Detailed information on the pediatric patients of village K was collected from files of the Child Neurology and Development Center and the Pediatric Department, Carmel Medical Center, Haifa. Patients were referred to these centers by health care clinics in the village for assessment of their neurological manifestations. Complementary data surveys of all neuropediatric-related hereditary disorders in this village were obtained from the local authorities, including: health care clinics, medical records from hospital departments, special education schools, and the government ministries of health and welfare.

2.3. Clinical Investigations and Classification of MR Cases

We investigated the etiology of MR-affected individuals by scrutinizing the medical diagnostic reports, which had been based on comprehensive physical and neurological examinations. In evaluating these reports we focused on the detection of dysmorphic features, minor anomalies, malformations and neurologic abnormalities. Patients with MR were divided into three major categories: (a) non-syndromic moderate to severe MR; (b) syndromic moderate to severe MR; and (c) mild MR and developmental delay.

2.4. Consanguinity

Information on consanguinity between the parents was obtained through personal interviews. Relationships were grouped into two major categories: consanguineous and non-consanguineous marriages, defined as follows:

Consanguineous marriage. This group includes two main classes of relationships: (a) First cousins and closer. These include double-first cousins (in which all grandparents are shared) and first cousins in which the couple are parallel or cross cousins of either patrilineal or matrilateral descent; (b) Distant relative marriages, in which the couple were relatives but not first-degree relations, for example they were first cousin once removed, second cousin, second cousin once removed.

Non-consanguineous marriage. The couple is not related.

Table 1. Total Numbers of Mentally Retarded Offspring from Consanguineous and Non-Consanguineous Marriages in Five Selected Villages.

Village	Number of affected children (Prevalence per 1000 children)	Consanguineousn (%)			Non-consanguineousn (%)	p
		Total	FC	DR		
A	32 (11.8)	20 (62.5)	15 (46.9)	5 (15.6)	12 (37.5)	0.157
B	48 (10.4)	34 (70.8)	27 (56.3)	7 (14.5)	14 (29.2)	0.004
C	55 (11)	37 (67.3)	32 (58.2)	5 (9.1)	18 (32.7)	0.022
D	92 (21.9)	66 (71.7)	58 (63)	8 (8.7)	26 (28.3)	0.00
K	73 (17.5)	48 (65.8)	40 (54.8)	8 (11)	25 (34.2)	0.007
Total	300 (14.5)	205 (68.3)	172 (57.3)	33 (11)	95 (31.7)	0.028

FC, first cousins; DR, distant relatives

Table 2. Distribution of Mental Retardation Spectrum Disorders in Village K.

Category of mental retardation	Number of families	All siblings aged between 0 and18 years in the families	Number and percentage of affected children (%)
Non-syndromic moderate-to- severe MR	10	56	23 (41)
Syndromic moderate-to- severe MR	11	36	18 (50)
Mild MR and developmental delay	18	59	32 (54.2)
Total	39	151	73 (48.4)

MR, mental retardation

2.5. Data Analysis

The SPSS program was used for data management and statistical analysis. The statistical significance of associations between consanguinity and various MR-spectrum disorders was examined by means of the χ^2 test.

3. Results

A total of 300 children were found to have MR, comprising an overall prevalence of 14.5 per 1000 children sampled. Table 1 shows that the prevalence of MR in the five villages ranged from 10.4 to 21.9 per 1000 children. The total numbers of children with MR of varying degrees (separated into those from consanguineous and from non-consanguineous marriages) in the five selected villages are also presented in Table 1. The majority (68%) of children with MR was found to be products of parental consanguinity; of these, 57% were the offspring of first cousins or closer and 11% were offspring of distant relatives. Approximately 32% of the affected children were born to unrelated couples. The difference between the prevalence of MR in children of consanguineous and non-consanguineous parents was significant ($p < 0.05$) in all the studied villages except for village A ($p = 0.157$), indicating that there is a significant association between consanguinity and MR-spectrum disorders, and that genetic factors are probably the underlying cause.

In village K, a detailed survey was undertaken to determine the types and prevalence of MR-spectrum disorders and their association with parental consanguinity. Of the 9,315 inhabitants in the village, 4,166 (44.5%) were children below the age of 18. In this age group, 180 cases (4.3%) were affected by neurologically related hereditary diseases. Of these, 19 children had died (reflecting a mortality rate of approximately 10%), five had no specific diagnosis ascribed to them, and one child had moved out of the village. Of the remaining children, 86 boys (56%) and 69 girls (44%), 73 were found to have MR (47.1%), reflecting an overall prevalence of 17.5 per 1000 children. In 68.2% of the children with neurologically related hereditary disease, and in 65.8% of all children with MR, the parents' marriage was consanguineous.

Table 2 records the numbers and prevalence of MR-spectrum disorders among all the siblings aged 0 to 18 in the presented families. The data show that approximately 48% (73 cases) of the siblings from all 39 families had MR. Mild MR and developmental delay were found in 54% (32 children) from 18 families while syndromic moderate to severe MR were found in 50% (18 children) from 11 families and non-syndromic moderate to severe MR were found in 41% (23 children) from 10 families.

Table 3 records selected characteristics of children with MR. The prevalence of MR was higher in boys (59%) than in girls (41%). The detailed age distribution

Table 3. Age and Gender of Children with Mental Retardation in Village K.

Age(years)	Children with mental retardation			
	Non-syndromic moderate-to-severe MR	Syndromic moderate-to-severe MR	Mild MR and developmental delay	Totaln (%)
< 5	5	7	13	25 (34.3)
> 5–10	6	5	12	23 (31.5)
> 10–15	6	4	5	15 (20.5)
> 15	6	2	2	10 (13.7)
Total n (%)	23 (31)	18 (25)	32 (44)	73 (100)
Gender				
Male	14	11	18	43 (59)
Female	9	7	14	30 (41)

MR, mental retardation

Table 4. Prevalence of Mental Retardation Spectrum Diseases Disorders in Village K of Offspring from Non-consanguineous Marriages and Different Degrees of Consanguineous Marriages.

Category of mental retardation	Affected siblings n	Consanguineousn (%)			Non- consanguineousn (%)	p
		Total	FC	DR		
Non-syndromic moderate-to-severe MR	23	18 (78.3)	15 (65.3)	3 (13)	5 (21.7)	0.001
Syndromic moderate-to-severe MR	18	11 (61.1)	11 (61.1)	0	7 (38.9)	< 0.001
Mild MR and developmental delay	32	19 (59.4)	14 (43.8)	5 (15.6)	13 (40.6)	0.078

MR, mental retardation; FC, first cousins; DR, distant relatives

recorded in the table shows that the majority (66%) of children with MR was in the 1- to 10-year age group. Prevalence of the various MR-spectrum disorders among the affected children was 44% (32 cases) of mild MR and developmental delay; 25% (18 cases) of syndromic moderate to severe MR, and 31% (23 cases) of non-syndromic moderate to severe MR.

Table 4 compares the prevalence of MR-spectrum disorders among the offspring from the three categories of consanguinity in village K. The majority (66%) of the children with MR were the outcome of consanguineous marriages: in 40 of 48 cases (84%) their parents were first cousins, and in 8 cases (16%) they were distant relatives. In 25 cases (approximately 34%) the parents of affected children were unrelated. Although the numbers are small, the results reflect significant differences in MR prevalence in the more severe categories (non-syndromic and syndromic moderate to severe) between the offspring of consanguineous and non-consanguineous parents ($p = 0.001$ and $p < 0.001$, respectively). Within the category of mild MR and developmental delay, in contrast to the above, children of consanguineous and non-consanguineous parents showed no significant differences in the prevalence of MR.

4. Discussion

The prevalence of MR in the general population has been estimated at 1% to 3% [9]. A strong association of MR with low socioeconomic status has also been demonstrated [18]. The prevalence of MR among pediatric populations is varying in different countries between 6.2 per 1000 children (in Norway; [16]), to 84 per 1000 children (in Pakistan; [17]). In the villages selected for the present study we found that MR affected, on average, 14.5 per 1000 children, and ranged from 10.4 to 21.9 per 1000 children. These findings indicate that MR in the studied population is considerably more prevalent than in western societies, although lower than in some developing countries [16-18]. The present finding of high MR frequency relative to that in western countries is evidently attributable to the high rate of consanguinity. However, the Israeli Arab community is currently going through a positive transition process, with ongoing improvements in the preventive and medical health care systems that probably account for the lower prevalence of MR found here than in some countries.

Nevertheless, despite the previously reported decrease in the rate of consanguineous marriages within the Israeli Arab community [6,19], consanguinity is still the most common risk factor for a high frequency of rare autosomal recessive diseases and congenital

malformations within this community [1,14]. A strong association between MR and consanguinity was demonstrated by the present finding that approximately 68% of children with MR were the offspring of consanguineous marriages, and that in approximately 84% of these marriages the parents were first cousins or closer.

The prevalence of MR in Village K was studied in more detail. Approximately 48% of the siblings of the affected families in this village were found to have MR and most of them (67% of cases) were aged between 0 and 10 years. As in the other villages, consanguinity in village K was a major risk factor for the occurrence of MR-in the offspring. Moreover, the risk of non-syndromic moderate-to-severe MR in children of consanguineous parents was significantly higher than in children of non-consanguineous parents (78% vs. 22%). Based on the results of this study, we plan to intensify our efforts to identify the mutation(s) responsible for these genetic diseases so that a preventive program can be launched, with the aim of minimizing the occurrence of MR-spectrum disorders in future generations.

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