

The pattern of inherited microcephaly and role of the consanguineous marriage: A study from Southwestern Iran

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Abstract

Background: Microcephaly is a congenital disorder characterized by a head circumference falling more than two standard deviations below the mean with respect to age- and gender-matched population sample, which is divided into isolated and syndromic types. This study aimed to show the inheritance pattern of microcephaly and role of the consanguineous marriage in Southwestern Iran.

Patients and Methods: In this study, medical records of 1202 people (out of 3951 families, 30.4%) with autosomal recessive pattern inherited disorder who attended the centers of Khuzestan state welfare organization, southwestern Iran during 2011 to 2016 for genetic counseling, were reviewed.

Results: Overall, out of 1202 cases of microcephaly, 114 (9.48%, 2.3/100,000 live births) people were detected. The results showed that most patients were female (66.7%), from Arab ethnicity (63%). Most of the patient's fathers were at the level of primary school education (63%) and self-employed (63%), while patient's mothers completed primary school education (37%) or illiterate (37%) and housewife (100%). Income distribution showed that the majority of families were below the poverty line (63%), and lived in the urban area (37%). The study showed that the frequency of consanguineous marriage was much higher (81.5% vs. 18.5%, $P=0.0013$).

Conclusion: In as much as lack of access to early medical attention, poor socio-economic state and harsh environmental factors affect mental health response, these factors are believed play crucial role in reducing the incidence of mental health and associated abnormalities. Considering the relatively high prevalence of inherited microcephaly, it is important to set up clinical guidelines for early detection and management of these conditions to decrease the associated morbidity and mortality. [*Ethiop. J. Health Dev.* 2017;31(2):119-123]

Keywords: Inherited microcephaly; consanguineous marriage; Southwestern Iran

Introduction

Microcephaly is a congenital disorder characterized by a head circumference falling more than two standard deviations below the mean with respect to age- and gender-matched population sample, which is divided into isolated and syndromic types (1). Recent evidence reported that microcephaly is a primary disorder of the neurogenic mitosis (2); therefore, the brain and, consequently, the skulls are smaller than the community normal size (3).

Microcephaly is divided into isolated (non-syndromic) and syndromic types (primary, resulting from the slowdown and non-progressive brain development and secondary, resulting brain damage). Most of the autosomal recessive primary microcephaly has a normal weight, height, appearance, chromosomal analysis and brain scan (4).

Consanguineous marriage is defined as when the first-degree relatives are married to each other, and recent reports revealed that one billion of the existing worldwide population has a preference for consanguineous marriage (5-7). Though, consanguineous marriage is a more prevalent feature of family systems in south-west Asia, Middle East,

especially Iran, its prevalence is slowly declining (8-11). The prevalence of primary microcephaly is ranged from 1.3 to 150 per 100,000 people depending on the type of population used to define microcephaly (3, 12, 13). The prevalence of primary microcephaly is more in Asians and Arabs than whites, as well as it is more common in consanguineous populations (4, 14, 15). It was suggested that in India 1 in 4348 births will be affected by microcephaly, which means 5887 babies with microcephaly will be born in India every year (16). An average of 157 cases of microcephaly were detected each year in Brazil (17). The prevalence of microcephaly was estimated as 1.53 per 10 000 births in Europe (18). The limited knowledge of the epidemiological surveillance data about the microcephaly outbreak as well as other aspects of the epidemic, associated with its relatively fast evolution, emphasize the need for critical examination of the relationship between microcephaly and the role of the consanguineous marriage.

To the best of our knowledge, there is no data about the pattern of inheritance of microcephaly and the role of the consanguineous marriage as well as the need for research and implementing clinical prenatal diagnosis

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programs in Southwestern Iran. Given a very high level of consanguineous marriage in southwestern Iran community as well as much of the increased risk of birth defects such as microcephaly in the offspring of consanguineous marriages; we aimed to reveal the pattern of inheritance of microcephaly and the role of the consanguineous marriage in Southwestern Iran.

Methods

Study design and population: Genetics counseling centers of Khuzestan State Welfare Organization were established in 2006. During April 2011 through March 2016, more than 3951 families attended these centers for genetics counseling. Centers of Khuzestan State Welfare Organization is the referral site for most of the medical services, follow ups, and monitoring in this region. In this study, medical records of 1202 people (out of 3951 families, 30.4%) with autosomal recessive pattern inherited disorder who attended the centers of Khuzestan State Welfare Organization, southwestern Iran during 2011 to 2016 for genetic counseling, were reviewed. This research was approved by the ethics committee, Khuzestan Welfare Organization.

Data undercover Khuzestan Welfare Organization: Khuzestan Welfare Organization composes of 3 main fields, including rehabilitation with 15 centers, social with 29 centers and prevention with 7 centers across the province. The Khuzestan Welfare Organization has two main tasks, which give services in the fields of rehabilitation, social and disability prevention. In the social field only covered nearly 33 thousand households. Nearly 70 thousand people with disability registered in the Khuzestan Welfare Organization so far, as well as 16 thousand households receive directly pension from this Organization.

Procedures and Data collection: Two of the authors (F.R. and A.S-M) reviewed the files. The information about referral reason, consanguinity, ages of the couple, and type and frequency of various abnormalities recorded in the pedigrees were collected. To determine the prevalence of microcephaly, as the proportion of current cases of microcephaly at a specified time, the population of the Khuzestan province (Southwestern Iran) was considered according to the 2016 Census of the Statistical Center of Iran as 510000; thus, the prevalence was calculated considering the population who had microcephaly on 510000 people in 2016. Globally, a positive correlation between disease prevalence and poverty was reported, whether this is evaluated by Human Poverty Index (HPI), income inequality, or gross domestic product per person (19, 20). The association of poverty with increased prevalence of a specific disease has described through many reasons, including increased biological susceptibility, malnutrition, lack of access to health care, lack of education, and illiteracy, but does not necessarily

indicate a causal relation (21-23). The poverty line in Iran varies from one province to another considering different components such as a certain households consumer basket. The poverty line of southwestern Iran was reported as 15 million rials ((US\$467) a month (24).

Statistical analysis: SPSS software version 15 was used. In case of testing the association between type of disease and main risk factors Chi-square test was used. A P-value less than 0.05 was considered as significant difference. Pearson correlation was used to assess the correlation between variables of interest and microcephaly. We also calculated unadjusted Odds Ratio (OR) along with 95%CI (confidence interval) according to Reichenheim and Coutinho method using the prevalence odds ratio and related binary logistic regression models with main risk factors for causal inference in cross-sectional studies (25).

Ethical considerations: This research was approved by the ethics committee of welfare organization, Ahvaz. All the participated subjects were signed informed consent prior to enrollment. The results were strictly confidential and were used solely for research purposes and the patient's identity remained confidential.

Results

Basic characteristics of the study patients were listed in table 1. Overall, out of 1202 cases of microcephaly people 114 (9.48%, 2.3/100,000 live birth, considering the population of 5100000 of the area of interest based on the 2016 census) were detected. The results showed that most patients (66.7%) were female. Most patients were from Arab ethnicity (63%). The majority of fathers were educated to primary school level (63%), while mothers who reached to the level of primary school education were (37%) or illiterate (37%). The majority of fathers were self-employed (63%) and all mothers were housewife (100%). In the present study, income distribution showed that the vast majority of families were below the poverty line (63%). Overall, 106 families out of 114 (92.98%) were below the poverty line. The majority of families lived in urban areas (37%). The study showed that the frequency of consanguineous marriage in families who were undercover of welfare organization were significantly higher (81.5% vs. 18.5%, $P=0.0013$). In this study as expected, the incidence of congenital abnormalities and inherited microcephaly in a family with a history of disability was higher (63%). Microcephaly was inherited as an autosomal recessive pattern in most of the cases (110 cases, 96.5%, Table 1). Most of the families were under poverty line (106/114, 92.98%), but there was a weak positive correlation and the probability between poverty line and microcephaly ($r=0.233$, OR (95%CI): 1.38 (0.32 – 6.15), Table 2).

Table 1: Demographic variables in the study group

Demographic Variables		N (%)
Gender	Male	38 (33.3)
	Female	76 (66.7)
Ethnicity	Fars	30 (25.9)
	Arab	72 (63)
	Lur	12 (11.1)
Education	Illiterate	25 (22.2)
	Primary school	72 (63)
	Diploma	17 (14.8)
Father's education	Illiterate	42 (37)
	Primary school	51 (44.4)
	Diploma	21 (18.5)
Mother's education	Illiterate	42 (37)
	Primary school	42(37)
	Diploma	30(26)
Father's job	Unemployed	13 (11.1)
	Self-Employed	97 (85.2)
Mother's job	Employed	4 (3.7)
	Housewife	114 (100)
Income, Iranian Rial	<1*10 ⁷	70 (63)
	1*10 ⁷ -1.5*10 ⁷	36(29.6)
	1.5*10 ⁷ -2*10 ⁷	8(7.4)
Residency	Urban	93(81.5)
	Rural	21(18.5)
Consanguineous marriage	Yes	93(81.5)
	No	21(18.5)
Type of disability	Inherited	106 (92.6)
	Congenital infections during pregnancy	8 (7.4)
Pattern of inheritance	Autosomal recessive	110 (96.5)
	X-linked	4 (3.5)
Family history of disability	Yes	72 (63)
	No	42 (37)
Age at diagnosis, Mean ± SD	3.41 ±1.62	(1-6)
Age, Mean ± SD	9.04 ±3.77	(3-16)
Total	114 (100)	

The frequency of isolated microcephaly was 5.66%, while the Syndromic type was 3.82% (Table 2). Comparing various consanguinity degrees showed that the probability of the birth of a child with isolated microcephaly in the 2nd and 3rd marriage were 3.46 higher than 4th degrees (Table 2).

Table 2: Frequency of various microcephalies and analysis of association with odds ratio estimate and 95% confidence intervals

Variables	Various microcephalies		P-values*	Total
	Isolated	Syndromic		
Gender				
Male	30	18		48
Female	38	28		66
Total	68	46	0.689	114
Consanguinity degree				
2 nd and 3 rd	37	20		57
4 th and over	10	19		29
Not-mentioned	21	7	<0.001**	28
Total	68	46	OR*** (95%CI): 3.46 (0.22 – 7.14)*	114
Poverty line (1.5*10⁷)				
Under poverty line	74	32		106
Over poverty line	5	3	0.6667	8114
Total	79	35	OR (95% CI): 1.38 (0.32-6.15)	
Overall frequency (out of 1202 cases)	5.66%	3.82%	-----	9.48%

* Chi Square test

**Between two first groups comparison in isolated type

*** Unadjusted OR calculated by binary Logistic

Discussion

This study aimed to reveal the inheritance pattern of microcephaly and the role of the consanguineous marriage as well as the need for research and implementing clinical prenatal diagnosis programs in Southwestern Iran. The frequency of inherited microcephaly was 9.48% (2.3/100,000 live birth). In line with this study, another study from the same region showed that less frequent inherited of microcephaly cases (5.51%) are indeed more likely to occur (26).

Our results indicate that the frequency of microcephaly was significantly higher in consanguineous marriage and this result confirmed by several studies. As a matter of fact, the risk of isolated microcephaly in the 2nd and 3rd marriage was higher than other consanguineous marriages (27). In Southeastern Iran, the studies have shown that 40% of Intellectual disabilities were from consanguineous families, in which microcephaly cases constitute 12% of this population (??). Also, another study from Northwestern Iran, reported the prevalence of microcephaly as 0.056/100,000 in consanguineous population(28).

The prevalence of microcephaly was also reported as 1/100,000 in consanguineous populations like Pakistan (29). Actually, several studies have shown a higher prevalence of congenital malformations, especially inherited microcephaly in consanguineous marriage (30-33). Since the rate of consanguineous marriages and related congenital malformations in the country and the province of interest are high, more specific diagnosis screening and management seems to be necessary. The possible explanation for differences in prevalence is the high rate of consanguineous marriage in the area of interest, of which higher inherited disabilities such as microcephaly have been reported in the consanguineous population.

This study also showed that the frequency of inherited microcephaly in Arab ethnicity was more than others. However, another study has reported that risk of the isolated microcephaly in non-Arab ethnic more than the risk in Arab ethnicity (27).

Usually, the poverty line is determined due to the economic and social characteristics of each region. Because of the diversity that exists in Iran and huge differences in levels of development in various regions of the country, we cannot consider a fixed poverty line for all regions across the country. In the present study, income distribution shows that the vast majority of families are below the poverty line. This finding may reveal that inherited microcephaly is more prevalent in low-income households. In agreement with our finding, a study from Kuwait reported higher prevalence of microcephaly in low-income families (34).

Conclusion

The study showed that the prevalence of isolated microcephaly was significantly higher in consanguineous marriage. In fact, consanguineous marriage played a detrimental role in causing high rates of malformation which microcephaly is one of them.

Furthermore, family histories of disability, congenital anomaly in any of the couple's family, a history of infertility or miscarriage among women over 35 years are important factors. The disease is more common in certain geographic areas. Since many mental disabilities are due to lack of access to early medical and health diagnosis and management as well as the role of environmental factors and socioeconomic status. Thus, the role of environmental factors and socioeconomic status may play a crucial role in reducing the incidence or abnormalities. Considering the relatively high prevalence of inherited microcephaly, it is important to establish clinical guidelines for early detection and management of these conditions to decrease the associated morbidity and mortality.

In case of pregnancy with consanguineous parents, it is recommended for counseling to estimate the risk of fetal inherited microcephaly, and diagnostic imaging at the gestational age of 11-14 weeks to detect an early malformation.

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