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Family history of diabetes among first cousins and the risk of ocular disorders in northern Morocco.

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Abstract

Muslim countries were the most concerned about consanguinity, and this practice can affect the genetic variability and increase the risk of multifactorial diseases. This study examines the impact of family history of diabetes among consanguineous individuals on the occurrence of ocular anomalies. This is an observational, cross-sectional study design carried out between 2017 and 2020 on a sample of 3600 students. The interviewed give information about their siblings, their parents and their grandparents' generation. Multivariable logistic regression analysis was used. Adjusting for sociodemographic variables, multivariate logistic regression model revealed that first cousin maternal grandparents (aOR=1.84, 95% CI: 1.41-2.39, p<0.001) and family history of diabetes (aOR=1.96, 95% CI: 1.24-3.10, p<0.01) were independent risk factors for diabetes among offspring. However, the cumulative effect of family history of diabetes and fist relatives' parents showed a higher risk (aOR=4.21, 95% CI: 1.86-9.52, p<0.01). A significantly higher risk of visual disturbances in the students or their siblings 3.14 (aOR=3.14; 95% CI: 1.31-7.52, p<0.05) was observed when parents were non-consanguineous and at least one of their offspring had diabetes. This risk became 6.58 times higher (aOR=6.58; 95% CI: 1.95-22.11, p<0.01) when parents were first cousins and students or their siblings had diabetes, controlling for all other variables. Cumulative effect of family history of diabetes and fist relatives' parents was an independent risk factor for diabetes and visual disturbances among progeny. Educational intervention and genetic counseling are needed to prevent these diseases among consanguineous new couples.

Keywords: Consanguinity, visual disturbances, first cousins, family history, diabetes.

Full length article **Corresponding Author*, e-mail: *mohamed.hajjaji4@uit.ac.ma*

1. Introduction

Consanguineous marriages include unions between third cousin couples or closer [1, 2]. In Morocco, the prevalence of consanguinity varies from region to another between 23.7% in the north of the country and 25.38% in the south. Unions between first cousins are the highest among other types of consanguineous marriages [3,4]. The relationship between the degree of consanguinity and the risk of the occurrence of congenital anomalies has been confirmed by several studies [5,6,7,8]. This relationship between consanguinity and the risk of genetic diseases development is proportional to the degree of consanguinity and the family history of individuals [7,9,10]. Homozygosity among consanguineous offspring increases some genetic disorders such as hypertension, ocular disorders and diabetes [11,12,13]. Most studies, examining the impact of consanguinity on the occurrence of diabetes and the ocular anomalies, confirm the increase of diabetes and ocular diseases among offspring of consanguineous couples [11,14,15,16]. The increase of those diseases correlate with consanguinity levels. Thus, the occurrence of diabetes and ocular disorders are higher when parents are first cousins [17,18,19]. The increased risk of diabetes among offspring is also associated with family history of diabetes [20]. Family history of diabetes and diabetes among individuals are common risk factors associated with the occurrence of ocular diseases [21,19].

The students recruited in this study were from the province of Tetouan. According to 2014 general census, the population was 550,374. To our knowledge, no studies, in Morocco, have examined the cumulative effect of diabetes or family history of diabetes among consanguineous individuals, especially first relatives, on the development of ocular anomalies. In this context, this study aimed to determine the influence of family history of diabetes and first-degree parental consanguinity on the development of ocular abnormalities in offspring.

2. Materials and methods

2.1. Research Design and Study Population

This was an observational cross-sectional study design conducted between 2017 and 2020 on a sample of 3600 students who volunteered to participate in the study, randomly selected from students enrolled at Abdelmalek Essaadi University in Tetouan. Taking into account ethical considerations, the study was approved by the participants' university and the research team took all possible ethical measures to ensure the protection of the participants. Students were later informed that they could withdraw from the study at any time without penalty and would remain anonymous and confidential throughout the study. The questionnaire included consanguineous marriages among parents and grandparents, demographic and pathological information.

2.2. Variables

2.2.1. Exposure

The types of consanguineous marriages among parents and grandparents are divided into three categories: first cousins, first cousins once removed and second cousins, parents and grandparents.

2.2.2. Outcome

The outcome variable for this research in the first model was diabetes in parents (i.e. non-diabetics vs Diabetics), in the second model was diabetes in the student or their siblings and visual disturbances in students or their siblings in the third model. Furthermore, respondents could not identify the exact type of diabetes, the reason for which we considered patients with all types of diabetes. The students or their siblings' visual disorders were also not specified by type of anomalies.

2.2.3. Sociodemographic characteristics and Covariates

The sociodemographic characteristics included father and mother's provenance (urban or rural provenance). Education status (illiterate, primary, secondary and superior) was the level of education of student's father, level of education of student's mother, level of education of student's paternal grandparents and level of education of student's maternal grandparents [22].

2.5. Statistical Analysis

In descriptive analyses, categorical variables were described as percentages and compared using the chi-square test. Values of $p<0.05$ were considered statistically significant. We estimated the prevalence rates and 95% confidence intervals of first cousin parents in various levels of consanguinity among parents and grandparents' groups. For the binary logistic regression model, the selection of explanatory variables was based on knowledge of diabetes and visual disturbances in offspring of consanguineous marriages and possible influencing factors. Therefore, variables potentially associated with diabetes among mothers or their sibling (model 1), and diabetes and visual impairment (model 2 and 3) in students or their siblings were introduced into the logistic regression. Variables were selected based on their clinical relevance and knowledge of proven or suspected confounders [23]. Then, explanatory variables that are closely related to the dependent variable are retained in the model. In the univariate analysis of parental consanguineous marriage or offspring risk of diabetes and visual impairment, all variables with a significance level less than 0.20 were included in the multivariate logistic regression models. A threshold of 0.20 allowed the inclusion of variables intended to represent possible confounders or interactions. Variables that were forced ($p > 0.20$) or known to be associated with both dichotomous responses were also included in the analysis. To determine the best model in mathematical modeling using logistic regression, we also focus on a strategy that consists of three stages: (1) variable specification, (2) interaction evaluation, (3) confounding evaluation, and then accuracy accounting [24]. The fit of the model was tested using the Hosmer-Lemeshow fit test. Odds ratios (OR) and 95% confidence intervals (CI) were calculated to determine whether exposure factors were significantly associated with dichotomous variables. The full model included simultaneous multivariable analysis (adjusted OR) of risk factors for diabetes and eye disease among close relatives' parents and grandparents.

The statistical software package Stata/MP V.14.1 (StataCorp) was used in this analysis.

3. Results and Discussions

3.1. Risk factors for diabetes in parents according to degree of grandparents' consanguinity.

Univariate and multivariate analyses of grandparents' consanguinity degree and diabetes in parents were presented in Table 1. Using univariate analysis, we found that first cousin maternal grandparents (cOR=1.83, 95% CI: 1.40-2.38, $p<0.001$) was a risk factor related to diabetes in mothers or their siblings. However, first cousins once removed maternal grandparents, second cousin maternal grandparents, first cousin paternal grandparents, first cousins once removed paternal grandparents and second cousin paternal grandparents were not risk factors for diabetes in this study. The positive outcome of univariate analysis was studded by multivariate regression analysis. Our multivariate logistic regression model adjusted for level of education of the student's paternal grandfather, level of education of the student's paternal grandmother, level of education of the student's father, father's provenance and mother's provenance showed that first cousin maternal grandparents (aOR=1.84, 95% CI: 1.41-2.39, $p<0.001$) was an independent risk factor for diabetes in mothers or their siblings. The relationship between the degree of consanguinity and the risk of congenital anomalies has been confirmed by multiple studies [6,8,9,25]. The excessive homozygosity observed in genetic diseases is caused by consanguineous marriage [26]. In Iran, more than 50% of children with genetic abnormalities have consanguineous parents [27]. Various studies have highlighted the association between consanguineous mating and diabetes [11,28,29]. Our findings indicate that first-degree grandparents was an independent risk factors for diabetes in mothers or their siblings. Albishi et al. (2022) reported that in Saudi Arabia, the incidence of type 1 diabetes was higher in offspring of first cousins than in offspring of second cousins [17].

Table 1: Univariate and multivariate logistic regression analysis of diabetes in parents and their siblings among grandparents' consanguinity.

Degree of consanguinity	Diabetes in fathers or their siblings[Dv]		Diabetes in mothers or their siblings[Dv]	
	Paternal grandparents		Maternal grandparents	
	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
	cOR (95% CI)	aOR (95% CI) φ	cOR (95% CI)	aOR (95% CI) ɤ
Non-consanguineous	Reference	Reference	Reference	Reference
First cousins	1.18 (0.87-1.61) NS	1.16 (0.85-1.57) NS	1.83 (1.40-2.38) ***	1.84 (1.41-2.39) ***
First cousins once removed	1.14 (0.83-1.56) NS	1.13 (0.82-1.56) NS	1.16 (0.64-2.08) NS	1.18 (0.66-2.12) NS
Second cousins	1.09 (0.71-1.66) NS	1.09 (0.71-1.66) NS	0.90 (0.68-1.20) NS	0.90 (0.67-1.20) NS

φ : Model adjusted for level of education of the student's paternal grandfather, level of education of the student's paternal grandmother, level of education of the student's father, father's provenance and mother's provenance.
ɤ: Model adjusted for level of education of the student's maternal grandfather, level of education of the student's maternal grandmother, level of education of the student's mother and mother's provenance. cOR: crude odds ratio, aOR: adjusted odds ratio, CI: confidence interval, ***p < 0.001; Dv: dependent variable.

Table 2: Multivariate logistic regression analysis of diabetes in students or their siblings among parents' consanguinity.

Diabetes in the students or their siblings[Dv]		
	Univariate analysis	Multivariate analysis
	cOR (95% CI)	aOR (95% CI) ɷ
Non-consanguineous parents		
Diabetes in mothers or their *siblings*		
No	Reference	Reference
Yes	1.98 (1.25-3.12) **	1.96 (1.24-3.10) **
Diabetes in fathers or their *siblings*		
No	Reference	Reference
Yes	0.46 (0.22-0.97) *	0.43 (0.22-0.97) *
First cousin parents		
Diabetes in mothers or their *siblings*		
No	Reference	Reference
Yes	4.29 (1.95-9.49) ***	4.21 (1.86-9.52) **
Diabetes in fathers or their *siblings*		
No	Reference	Reference
Yes	1.10 (0.49-2.43) NS	1.01 (0.44-2.29) NS

ɷ : Model adjusted for level of education of the student's father, level of education of the student's mother, father's provenance and mother's provenance. cOR: crude odds ratio, aOR: adjusted odds ratio, CI: confidence interval, *p < 0.05, **p < 0.01, ***p < 0.001; Dv: dependent variable.

Table 3: Multivariate logistic regression analysis of visual disturbances in students or their siblings among parents' consanguinity.

Visual disturbances in students or their siblings[Dv]		
	Univariate analysis	Multivariate analysis
	cOR (95% CI)	aOR (95% CI) ʊ
Non-consanguineous parents		
Diabetes in students or their siblings		
No	Reference	Reference
Yes	3.22 (1.35-7.66) **	3.14 (1.31-7.52) *
First cousin parents		
Diabetes in students or their siblings		
No	Reference	Reference
Yes	5.41 (1.74-16.85) **	6.58 (1.95-22.11) **

ʊ : Model adjusted for level of education of the student's father, level of education of the student's mother, father's provenance and mother's provenance. cOR: crude odds ratio, aOR: adjusted odds ratio, CI: confidence interval, *p < 0.05, **p < 0.01; Dv: dependent variable.

3.2. Risk factors for diabetes in the students or their siblings according to family History of diabetes and parents' consanguinity.

Using binary logistic model (Table 2), for degree of parents' consanguinity stratified by diabetes, we found that diabetes in mothers or their siblings when parents were non-consanguineous was positively associated with diabetes in the students or their siblings (cOR=1.98, 95% CI: 1.25-3.12, p<0.01), while the OR for diabetes in the students or their siblings was higher (cOR=4.29, 95% CI: 1.95-9.49) when mothers or their siblings were diabetics and parents were first cousins. When fathers or their siblings had diabetes and parents were non-consanguineous, a negative association was observed between the family history and the occurrence of diabetes in the students or their siblings (cOR=0.46, 95% CI: 0.22-0.97, p<0.05). After adjusting the model for level of education of the student's father, level of education of the student's mother, father's provenance and mother's provenance, we found similar results. After adjusting for confounders, the occurrence of diabetes in students or their siblings was high (aOR=1.96, 95% CI: 1.24-3.10, p<0.01) when parents were not consanguineous and mothers or their siblings were diabetic. In Pakistan, family history of diabetes is a risk factor of diabetes among adults [20]. In the same country, the risk of type 2 diabetes increases 3.94 times with a positive family history [30]. It has also been reported that family history of Type 1 diabetes increases the risk of this disease among progency in Qatar and Saudi Arabia [17,31]. The risk of diabetes in students or their siblings became 4.21 times (aOR=4.21, 95% CI: 1.24-3.10, p<0.01) higher when parents were first cousins and mothers or their siblings were diabetic. In Algeria, the main risk factors associated with type 2 diabetes are consanguinity and family history; consanguinity among parents increase this risk 3 times and the presence of type 2 diabetes among family increases it twice [32]. Similarly, the incidence of diabetes is 3 times higher among first cousin offspring with a positive family history of diabetes in Pakistan [33]. Among overweight or obese Yemeni individuals, a family history of diabetes and parental consanguinity increase the risk of pre-diabetes and diabetes [15].

3.3. Risk factors for visual disturbances in the students or their siblings

In the third model (Table 3), results revealed that, when students or their siblings have at least one case of diabetes and parents were non-consanguineous and when students or their siblings have at least one case of diabetes and parents were first cousins, the odds of visual disturbances were 3.22 and 5.41 (95% CI: 1.35-7.66, and 95% CI: 1.74-16.85, p<0.01), respectively. However, adjusting the model for level of education of the student's father, level of education of the student's mother, father's provenance and mother's provenance, the results remained almost the same as the univariate analysis (aOR=3.14, 95% CI: 1.35-7.66, and OR=6.58, 95% CI: 1.74-16.85, p<0.01, respectively). Thus, our results comply with previous studies confirming the relationship between diabetes and the occurrence of various visual diseases [18,19,34,35]. In a Mendelian randomization study, Chen et al in 2023 suggest that type 2 diabetes causes visual conditions such as Senile cataract, Glaucoma, and disorders of optic nerve and visual pathways [21]. In this study, the risk became 6.58 times higher when parents were first cousins and at least one of their offsprings had diabetes. Recent studies confirm this relationship between consanguinity and the occurrence of visual disorders in Turkey [14], in Togo [36] and in Iran [16]. In India, a high proportion of consanguineous marriage increases visual anomalies that cause visual impairment in early life decades such as endothelial dystrophy, corneal macular dystrophy, xeroderma pigmentosum, and ocular albinism [37]. An association of consanguinity, especially uncle-niece unions, with the occurrence of congenital ocular abnormalities among progency in south India was confirmed [38].

This high risk of visual disturbances among consanguineous can be explained, on one hand, by the fact that consanguinity contributes to an excess of homozygosity leading to an increased risk of genetic anomalies [2]. Molecular analysis revealed that affected patients with ocular abnormalities are carrying a homozygous pathogenic genetic variant in specific regions of some new candidate genes [39,40,41]. According to Salah et al (2023), this homozygosity related to ocular abnormalities is a result of consanguineous marriage between two heterozygous carriers of the deletion in chromosome 22q11.2 [13]. On the other hand, the existence of multifactorial diseases such as hypertension and diabetes related to consanguinity among parents increases the risk of those visual disturbances [42,43].

4. Conclusions

The inheritance of first cousin marriages from generation to generation leads to an excess risk of genetic disorders. Thus, our study suggests that cumulative effect of family history of diabetes and fist relatives' parents is an independent risk factor for diabetes and visual disturbances among offspring in Tetouan province. Educational intervention and genetic counseling are solicited to prevent diabetes and visual disturbances among consanguineous new couples.

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