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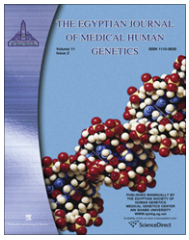

ORIGINAL ARTICLE

A study of new potential risk factors for Down syndrome in Upper Egypt

Hatem M.A. Shalaby *

Pediatric Department, Sohag University, Egypt

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Abstract Down syndrome is a common chromosomal anomaly causing multiple congenital malformations and mental retardation (MR) in humans. The well-established risk factor, advanced maternal age, was not found in many of the Down syndrome cases in Egypt, while other possible risk factors have not been well studied yet. In view of this, we have conducted the present study to clarify that issue and throw some lights on other potential risk factors in Down syndrome. During this cross sectional study, conducted during the period between March 2006 and Feb 2008, 48 clinically suspected cases of Down syndrome aged between 6 months and 9 years were referred for chromosomal investigation (karyotyping) from the outpatient and inpatient sections of the pediatric department, University Hospitals at the Upper Egyptian governorate Sohag. Chromosomal study was done in those patients after obtaining an informed consent. Twenty apparently healthy children were randomly selected as controls. Statistical study was carried out using logistic regression analysis. Out of the 48 cases of Down syndrome, 45 had free trisomy 21, two were mosaic trisomy 21, and one had translocation. Logistic regression of case-control study of Down syndrome children revealed that the odds ratio of uncle–niece marriages, or second cousin marriages, or parents lived in rural region, or exposure of the parents to drugs or chemicals, or parents education status, or habits (cigarettes/coffee used) of father, or mother not undergone ante-natal scanning as a part of ante-natal care, or mothers with previous abortions were significant when all the variables of that category were used one at a time. Besides the known risk factors, consanguinity, region (rural/urban) of residence of parents, exposure of parents to chemicals, educational status of parents,

* Tel.: +20 1050467474; fax: +20 932312755.
E-mail address: hatshal2006@yahoo.com

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habits of father, prenatal scanning, and reproductive performance of mother are possible risk factors for Down syndrome.

1. Introduction

Chromosomal abnormalities are common in human reproduction. Meiotic non-disjunction is the major mechanism responsible for the majority of aneuploidies in embryos [1].

Down syndrome (DS), the most frequent autosomal aneuploidy, causes mild to moderate mental retardation and occurs in one out of 600–800 live births, with an extra chromosome 21 due to non-disjunction [2,3].

Most of the aneuploidies that are maternal-age dependent are generated during meiosis I stage of oogenesis [4].

It is recently stated that not only the maternal age, but also some additional risk factors for this multifactorial trait will be identified and progress toward understanding the effect of maternal age on the meiotic process will be made given the advances in technology, publicly available genomic resources, and interdisciplinary approaches to these important studies [5].

Grand-Maternal Consanguinity is a possible predisposing factor for 21 trisomy (Down syndrome) in Young Mothers [6]. It has also been shown that older men produce more sperm with aneuploidy [7].

Although the relation of advanced maternal age to an increased risk of Down syndrome has been established, there are few studies on the effects of other risk factors [8].

Though a tremendous research work has been done on Down syndrome over the last few decades, most of the results obtained on etiological and demographic factors were based on Western data. The situation in Upper Egypt is entirely different; a high degree of consanguinity in various areas, along with a high population count provides an excellent opportunity for birth defect investigation.

In view of this, we report here in this cross-sectional study some other possible/potential risk factors for Down syndrome in Sohag governorate, Upper Egypt.

2. Subjects and methods

Over 2 years, during the period between March 2006 and Feb 2008, A cross sectional study in Down syndrome has been conducted, 48 clinically suspected Down syndrome were referred to the genetic laboratory for chromosome investigation (karyotyping) from the outpatient and inpatient sections of the pediatric department of Sohag University Hospitals. Informed consents were obtained from the parents of the studied children before inclusion in the study. Twenty randomly selected healthy children belonging to different localities in and around the city of Sohag, were used as controls. A genetic register was established by collecting complete information on the patients and control families. With this information, the pedigree of the families under study was constructed.

Logistic regression analysis was performed using the software ''Statistical Package for the Social Sciences'' (SPSS) version 10.0, to record the effect of the variables. Case-control status was used as the dependent variable and consanguinity, habits, region of residence, exposure to chemicals, educational status of parents, reproductive performance of mother, and prenatal scanning as the covariates. Results were reported as odds ratio from model with one variable at a time.

Informed consent was obtained from parents of the children.

This work was done after approval of ethics committee.

3. Results

Out of 48 cases of Down syndrome, 45 had free trisomy 21, two had mosaic trisomy 21, and one had translocation. A total of seven different possible risk factors were assessed in both the Down syndrome cases and the 20 apparently healthy children that were serving as controls.

Fig. 1 shows the distribution pattern of seven risk factors in cases of Down syndrome and controls. It shows the results of the previous 18 assessments done of the studied possible risk factors for Down syndrome as follows:

- Consanguinity
  - a = first cousin
  - b = uncle–niece
  - c = second cousin
  - d = far relatives
- Region of residence
  - e = rural
  - f = urban
- Exposure of parents to drugs
  - g = father exposed to chemicals
  - h = mother exposed chemicals
  - i = father and mother exposed to chemicals
- Educational status of parents
  - j = father uneducated
  - k = mother uneducated
  - l = both uneducated
- Habits of the father
  - m = father smoking cigarettes
  - n = father drinking coffee
  - o = father both smoking and drinking coffee
- Prenatal (Ante-natal) scanning
  - p = mother not undergone prenatal scanning
- Reproductive performance of mother
  - q = mother with abortions
  - r = mother with still births

A clear difference can be observed between the families of studied cases and controls regarding the risk factors, such as the residence, educational status of parents, habits of father, and the reproductive function of mother (Table 1).

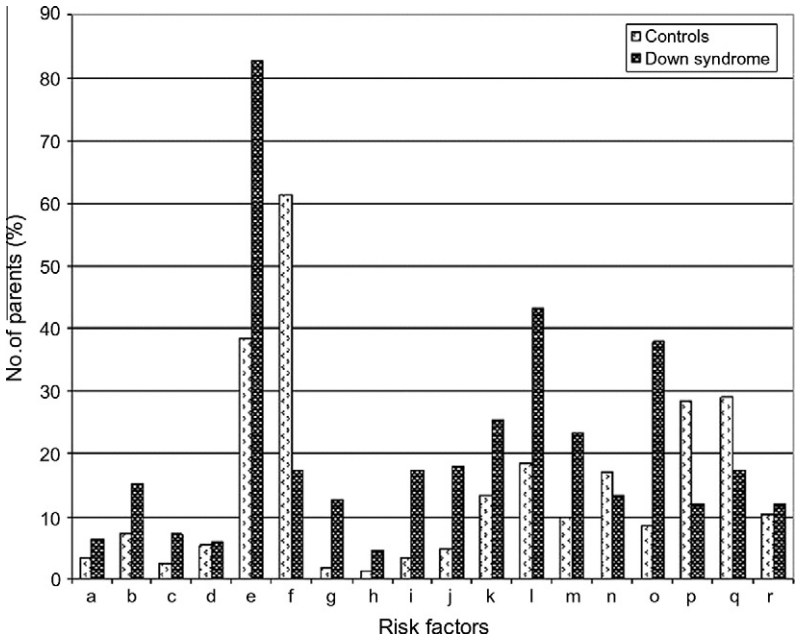

Figure 1 Distribution pattern of seven risk factors in the families of the studied cases of Down syndrome as well as controls. *Consanguinity*: a = first cousin, b = uncle–niece, c = second cousin, d = distant relatives; *Residence*: e = rural, f = urban; *Exposure of parents to drugs or chemicals*: g = father exposed to drugs or chemicals, h = mother exposed to drugs or chemicals, i = father and mother both exposed to drugs or chemicals; *Educational status of parents*: j = father uneducated, k = mother uneducated, l = both uneducated; *Habits of father*: m = father smoker, n = father drinking coffee o = father regular smoker and coffee user; *Ante-natal scanning*: p = mother not undergone prenatal scanning; *Reproductive function of the mother*: q = mother with abortions, r = mother with still births.

Table 1 The results of the logistic regression in the case-control study of Down syndrome children. The relationship of the seven risk factors with Down syndrome was analyzed by calculating the odds ratios (with the 95% confidence intervals).

Risk factors	Variables	Odds ratio (95% C.I)	*P* value
Consanguinity	First cousin	1.86 (0.7–5.2)	0.17
	Uncle–niece	2.3 (1.2–4.7)	0.02*
	Second cousin	3.6 (1.4–9.2)	0.04*
	Far relatives	1.2 (0.48–2.6)	0.82
Residence	Rural	7.2 (4.6–12.8)	0.0001*
	Urban	0.12 (0.08–0.23)	0.12
Drugs or environmental toxins	Mother	3.1 (0.7–11.8)	0.089
	Father	7.2 (2.48–22.6)	0.0001*
	Mother and father	5.6 (2.52–13.7)	0.0001*
Uneducated parent	Mother	2.22 (1.3–3.6)	0.0001*
	Father	4.3 (2.1–8.7)	0.0001*
Habits of father	Smoking cigarettes	1.8 (2.6–4.8)	0.002*
	Regular (daily) coffee drinking	0.6 (0.42–1.32)	0.28
	Both coffee and cigarettes	5.2 (2.6–9.4)	0.0001*
Antenatal scanning	Not done	3.6 (0.22–0.61)	0.0001*
Reproductive function	Abortion	0.52 (0.3–0.9)	0.01*
	Stillbirh	1.28 (0.62–2.8)	0.68

When each variable was examined separately, the odds ratios of the following factors were found to be statistically significant:

(a) Residence in rural area (*P* value 0.0001).
(b) uncle–niece and second cousin marriage (*P* value 0.02, and 0.04 respectively).
(c) Exposure of the father or both parents to drugs (*P* value 0.0001).
(d) Non educated parents (*P* value 0.0001).

(e) Habits of the father such as smoking or smoking plus regular (daily) coffee drinking (P value 0.002, and 0.0001 respectively).
(f) No prenatal scanning done (P value 0.0001).
(g) Past history of frequent abortions in the mother (P value 0.01).

4. Discussion

Advanced paternal age combined with advanced maternal age significantly influences the incidence of Down syndrome [9]. However there are contradicting reports regarding the maternal and paternal ages that increases the risk for chromosomal aneuploidy in Egypt [8].

Our findings had revealed that 36 cases (75% of the studied Down syndrome children) were born to young mothers, whose ages ranged from 17 to 28 years. The age distribution of the mothers as well as of the fathers of Down syndrome cases and controls indicates that both maternal and paternal age have no decisive influence on the manifestation of Down syndrome.

Malini and Ramachandra using Logistic regression analysis have revealed that the age of a maternal grandmother at the time of the birth of the mother is a risk factor for the occurrence of Down syndrome [10].

In our study we have reported the influence of other possible risk factors for Down syndrome as follows:

4.1. Consanguinity

The incidence of malformations was high in consanguineous marriages as compared to non-consanguineous marriages in Egypt [11].

In our study, the logistic regression analysis for consanguinity, using all the previously mentioned seven variables have shown that when these variables were considered one at a time, the effect of a consanguineous marriage to, for example, a first cousin or a distant relatives was diluted; however, still the effect of uncle–niece and second-cousin marriages were not diluted showing an increase in odds ratio by 22% and 6%, respectively. This supports the fact that consanguineous marriages between uncle and niece and between second cousins are risk factors for the manifestation of Down syndrome. However, it is known that consanguinity in Egypt is also influenced by population structure and socio-economic, ethnic, and religious factors.

4.2. Residence (urban or rural)

Verma et al. have reported that the frequency of congenital malformations is more in babies born to rural mothers than urban mothers [12]. They suggested that various factors, such as low socioeconomic status, environmental factors, and nutritional deficiency, could contribute to the increased incidence of malformations in rural areas. Their study indicated that medical awareness is essential for every parent, whether they belong to urban or rural regions.

In the current study, more Down syndrome children were born in rural areas than in urban areas. Logistic regression analysis using these as two covariates showed that when they were considered separately, the effect of urban residence was diluted but not that of rural residence, which showed an increase in odds by 64%.

4.3. Drugs or environmental toxins

Environmental toxins and drugs have the potential for inducing chromosomal non-disjunction [13]. In the present study, neither father nor mother was exposed to toxic chemicals, but they were exposed to drugs used for treatment of epilepsy, diabetes, hypertension, and other chronic diseases. Logistic regression analysis in our studied cases of Down syndrome using all the variables have shown that when these variables were considered one at a time, the effect of mother's exposure to drugs was not statistically significant, but the effect of the father's, as well as both parent's exposure to drugs was not diluted, showing an increase in odds by 10% and 76%, respectively.

4.4. Educational status of the parents

Various investigations have reported the strong relationship between education of the mother and the use of the health services for prenatal diagnosis [14,15]. In the present study, logistic regression analysis showed that when education of mother, education of father, and education of both parents were considered one at a time, none of the variables were diluted, showing an increase in odds by 14%, 16%, and 32%, respectively. Therefore, education appears to be an essential component in helping the parents to be aware regarding pregnancy care and the health of their progeny.

4.5. Habits of the parents

There are contradictory reports on the effect of cigarette smoking and regular (daily) coffee use on the occurrence of Down syndrome. [16–19] In Egypt, smoking and alcohol use is unusual among mothers. In the present study, common habits among the fathers: tobacco smoking, coffee drinking, and both coffee and smoking were found to be high in Down syndrome families. Logistic regression analysis using all the covariates have shown that when these variables were considered one at a time, the effect of regular coffee drinking in the father was diluted but the other effect of the other two covariates were not diluted, showing an increase in odds by 58% and 36%, respectively.

4.6. Ante-natal scanning

Several studies have documented the use of socioeconomic disparities, ethnicity, parity, and place of residence in prenatal diagnosis [20–22]. In the present study, although more number of mothers of Down syndrome children had undergone prenatal scanning than that of controls, the defect was not noticed. Generally, prenatal scanning was done to screen for gross anomalies. Logistic regression analysis using the variables has shown that when the covariate was considered one at a time, the effect of mother not having undergone prenatal scanning was not diluted, showing an increase in odds by 38%. Therefore, proper prenatal diagnosis has to be implemented in all the health-care centers both in rural and urban areas.

4.7. Reproductive function of the mother

The major issues in women's reproductive function are fertility regulation, abortion, maternal mortality, sexually transmitted diseases, and infertility. An increased risk of aneuploidy is present in women who have had many spontaneous abortions. Maternal health and reproductive potential have a prominent etiological significance in the occurrence of Down syndrome [23].

In the present study, the control mothers had more number of abortions than the mothers in Down syndrome. This finding supports the hypothesis that spontaneous abortions reduce the risk for chromosomal non-disjunction. Logistic regression analysis in our studied cases of Down syndrome using all the covariates have shown that when these covariates were considered together the effect of mothers reproductive performance, like mothers with abortions, was not diluted, showing an increase in odds by 51%.

During the present study, the following limitations were encountered. The information pertaining to parents was recorded during the data collection by interviewing the family members.

Although controls were selected randomly in different locations of Sohag governorate, and included all socio-economic groups, this selection cannot be absolute because some of the families did not give consent for investigations. These findings can be applied to the families with large progenies in Upper Egypt or elsewhere. Thus, besides the known risk factors, consanguinity, region of residence of parents, exposure of parents to chemicals, educational status of parents, habits of father, prenatal scanning, and reproductive performance of mother are all potential risk factors for Down syndrome.

5. Conclusion and recommendations

Advanced paternal and/or maternal age is a classic risk factor in Down syndrome, other risk factors include consanguinity, region (rural/urban) of residence of the family, Besides these risk factors, the exposure of parents to drugs/chemicals, the educational status of parents, the habits of father, ante-natal (prenatal) scanning, and the reproductive function of mother are potential risk factors for Down syndrome, and a proper ante-natal diagnosis has to be implemented in all the health-care centers both in rural and urban areas.

Conflict of interest

The authors declare that there is no conflict of interest.

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