A genetic epidemiological study of malformations at birth in Egypt

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دراسة وراثية وبائية حول التشوهات الخلقية عند الولادة في مصر

سامية علي التمتامي ونجوى عبد المجيد وإيناس مازن وسوزان رشدي إسماعيل ونبيلة صلاح الدين قاسم ورندة بسيوني

خلاصة : أجري تقييم شامل للحالة السريرية والوراثية لثلاثة آلاف طفل ولدوا على التوالي في مستشفى تخصصي للولادة بالجيزة بجمهورية مصر العربية . ومن بين البيانات الاجتماعية التي جُمعت عنهم درجة قرابة الوالدين والمستوى الاجتماعي . وقد وجد أن معدل حدوث التشوهات بين الثلاثة آلاف مولود حي أو ميت بالمستشفى يبلغ 3.17% . وتم تصنيف المواليد المشوهين (95) بحسب الجهاز الذي به التشوه إلى 13 مجموعة بحسب تصنيف منظمة الصحة العالمية للتشوهات الولادية . ووجد أن أكثر الشذوذات شيوعاً هي : الجهاز العصبي المركزي (29.5%) ، والجهاز الحركي 20.0% والمتلازمات الجينية (13.7%) . وكانت هناك قرابة بين الوالدين في 31.79% من جميع الحالات ، وفي 55.0% من الحالات المصابة بالتشوه ، الأمر الذي يؤكد ما لزواج الأقارب من آثار ضارة .

ABSTRACT A total of 3000 consecutive neonates delivered in a maternity hospital in Giza, Egypt, were subjected to full clinical and genetic evaluation. Social data included parental consanguinity and social class. The prevalence of malformations in the 3000 hospital live births and stillbirths was 3.17%. Malformed neonates (95) were classified into 13 groups according to the system affected using World Health Organization classification of congenital malformations. The most common anomalies were: central nervous system (29.5%), musculoskeletal system (20.0%) and genetic syndromes (13.7%). Parental consanguinity was found in 31.79% of all cases and in 55.0% of malformed cases, thus illustrating the deleterious effects of consanguinity.

Etude épidémiologique génétique des malformations à la naissance en Egypte
RESUME Un nombre total de 3000 naissances consécutives ayant eu lieu dans une maternité à Giza (Egypte) ont fait l'objet une évaluation clinique et génétique complète. Les données sociales comprenaient la consanguinité des parents et la classe sociale. La prévalence des malformations chez les 3000 enfants nés vivants ou mort-nés à la maternité était de 3,17%. Les nouveau-nés ayant des malformations (95) ont été classés en 13 groupes en fonction du système affecté en utilisant la classification des malformations congénitales de l'Organisation mondiale de la Santé. Les anomalies les plus courantes étaient les malformations congénitales du système nerveux central (29,5%), celles du système ostéo-articulaire et des muscles (20,0%) et les syndromes génétiques (13,7%). La consanguinité des parents a été décelée dans 31,79% de tous les cas étudiés et dans 55,0% des cas de malformations, ce qui démontre les effets délétères de la consanguinité.

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Introduction

Congenital malformations have been known and recognized for centuries. It is a stimulating problem for research study because of the high frequency of their occurrence and the devastating effect they may have on the individual and his/her family. Considerable variation in frequency in different populations has been reported, from as low as 1.07% in Japan [*1*] to as high as 4.3% in Taiwan [*2*]. This wide variability could be due to the different methodologies used in the different studies. In Egypt, the following results have been reported: 1.16% in Alexandria El-Shatby Hospital [*3*], 1.58% in Ain Shams University Hospital [*4*], 2.3% in Mansoura [*5*], 2.4% in Alexandria [*6*] and 1.3% in Mansoura and Ain Shams [*7*].

The primary objective of this study was to determine the prevalence of congenital malformations in neonates in Boulak El-Dakrour Hospital over a period of 2 years, and to classify the etiologies of malformations in neonates, whether of genetic or environmental origin, in order to allow proper genetic counselling, early management and rehabilitation.

Subjects and methods

The study included 3000 consecutive neonates delivered in Boulak El-Dakrour Hospital in Giza during the 2-year period, January 1991-April 1993. This hospital serves both urban and rural areas and was therefore chosen as an example of an average public health maternity hospital. Of 2925 deliveries, 3000 neonates were delivered i.e. 2851 singletons, 73 sets of twins and one set of triplets. Of the 3000 neonates, 39 were stillbirths and 18 died within the first 5 days of delivery. All the neonates were full term. They were examined at birth to identify major and minor congenital defects. Photographs, radiographs, necropsy reports and chromosomal studies were included when recommended. For each case with a congenital defect, the next non-malformed infant of the same sex born in the same hospital was selected as a control. Cases with genetic syndromes were diagnosed by review of *Mendelian inheritance in man* [*8*] and the *London dysmorphology database* [*9*]. Malformations were classified into systems according to World Health Organization (WHO) recommendations [*10*]. Every neonate was given a complete clinical examination. A sheet was completed for every neonate and control, including clinical, genetic and anthropological examination. Social data were obtained from the parents of the neonate, including educational level and occupation of the father and mother, parental consanguinity, number of children in the family and obstetric history. Anthropometric measurements were made according to the international biological programme [*11*]. They will be the subject of another report.

Results

The prevalence of congenital malformations in the 3000 hospital live births and stillbirths was 3.17% (31.67/1000 total births). The congenitally malformed neonates (95) were diagnosed and classified into 13 groups according to the affected system using *WHO* classification. The percentage was calculated from the total malformed number (95) and the per thousand figure from the total sample number (3000). Results were categorized as follows:

- central nervous system anomalies, 28 cases (29.5%, 9.33/1000)
- musculoskeletal anomalies, 19 cases (20.0%, 6.33/1000)
- genetic syndromes, 13 cases (13.7%, 4.33/1000)
- genital system anomalies, 8 cases (8.4%, 2.66/1000)
- miscellaneous, 6 cases (6.3%, 2/1000)
- cleft lip and/or cleft palate, 5 cases (5.3%, 1.66/1000)
- chromosomal aberrations, 4 cases (4.2%, 1.33/1000)
- more than one defect, 4 cases (4.2%, 1.33/1000)
- congenital heart disease, 3 cases (3.2%, 1/1000)
- ear, face and neck anomalies, 2 cases (2.1%, 0.66/1000)
- conjoined twins, 1 case (1.1%, 0.33/1000)
- gastrointestinal anomalies, 1 case (1.1%, 0.33/1000)
- urinary tract anomalies, 1 case (1.1%, 0.33/1000).

The frequency and distribution of the 95 birth defects are shown in Table 1. The commonest detected anomalies were those of the central nervous system (29.5%). Of the 95 affected neonates, 67 (70.53%) were live born and 28 (29.47%) were stillborn. Fourteen (14.74%) of the malformed infants died neonatally. Twinning was seen in 4 (4.21%) of the 95 cases. Eight cases (8.42%) had a history of affected relatives of the same or different condition. Single gene defects were responsible for 47 cases (49.5%), 44 cases (46.3%) were multifactorial in origin and 4 cases (4.2%) had chromosomal aberrations. Other important epidemiological results are shown in Tables 2 and 3. The data in the tables are explained in the discussion.

Discussion

In the present study, the prevalence of congenital malformations among 3000 hospital live births and stillbirths was 3.17% (31.67/1000 total births). This is much higher than previously reported in Egypt among live births and stillbirths: 1.16% in Alexandria [*3*], 1.58% in Cairo [*4*], 2.3% in Mansoura [*7*] and 2.4% in a recent study in Alexandria [*6*]. It is higher still than that reported in other populations (12.7/1000) in WHO centres in 16 countries [*3*]. Other studies among live-born neonates showed different prevalence figures: in Spain (20.23/1000) [*12*], in Libyan Arab Jamahiriya (23.8/1000) [*13*], in India (27.2/1000) [*14*]. On the other hand, the prevalence was lower than that reported previously from a hospital in Teheran (35/1000) for major congenital malformations and (88.4/1000) for minor and major malformations [*15*]. The prevalence in the present study is close to that noted in Atlanta, USA (31/1000) among live births only [*16*]. These variations in prevalence might be explained by social and racial influences which are commonly known in genetic disorders. Also, the results vary according to the background of the investigators and the type of sample studied.

In the present study, the number of stillbirths was 39/3000 (1.3%), and the number of malformed stillbirths was 28/95 (29.5%). This means that most of the severe congenital malformations were incompatible with life. Most of the malformed stillbirths in the present study were cases with central nervous system anomalies (71.4%). This is similar to the

Table 1 **Classification and distribution of malformed cases in 3000 Egyptian neonates**

Diagnosis	No. affected			% affected	Prevalence/1000
	M	F	Total		
Musculoskeletal					
Polydactyly (PAP)	2	–	2	2.1	0.666
Talipes equino varus	4	9	13	13.7	4.333
Talipes equino valgus	–	1	1	1.1	0.333
Syndactyly and polydactyly	2	1	3	3.2	1.000
Subtotal	8	11	19	20.0	6.332
Central nervous system					
Anencephaly	4	7	11	11.6	3.667
Craniorachischisis with bilateral talipes equino varus	–	1	1	1.1	0.333
Encephalocele	1	3	4	4.2	1.333
Hydrocephalus	3	7	10	10.5	3.333
Hydrocephalus and meningocele	1	1	2	2.1	0.666
Subtotal	9	19	28	29.5	9.332
Ear, face and neck					
Ear anomalies	–	2	2	2.1	0.666
Subtotal	–	2	2	2.1	0.666
Gastrointestinal tract					
Imperforate anus	1		1	1.1	0.333
Subtotal	1	–	1	1.1	0.333
Urinary tract					
Ectopia vesicae	1	–	1	1.1	0.333
Subtotal	1	–	1	1.1	0.333
Genital					
Ambiguous genitalia	–	1	1	1.1	0.333
Hypospadias	7	–	7	7.4	2.333
Subtotal	7	1	8	8.4	2.666
Congenital heart diseases					
Ventricular septal defect	1	1	2	2.1	0.666
Ectopia cordis	–	1	1	1.1	0.333
Subtotal	1	2	3	3.2	0.999
Cleft lip/palate	2	3	5	5.3	1.666
Subtotal	2	3	5	5.3	1.666
Genetic syndromes					
Aplasia cutis congenita	1	–	1	1.1	0.333
Chondrodysplasia punctata	1	–	1	1.1	0.333
Achondroplasia	1	–	1	1.1	0.333
Thanatophoric dysplasia	–	1	1	1.1	0.333
Osteogenesis imperfecta	1	–	1	1.1	0.333

Table 1 *(concluded)*

Diagnosis	No. affected			% affected	Prevalence/1000
	M	F	Total		
Holoprosencephaly	–	1	1	1.1	0.333
Freeman–Sheldon syndrome	–	1	1	1.1	0.333
Oto-palato-digital	1	–	1	1.1	0.333
Distal arthrogryposis	–	1	1	1.1	0.333
Arthrogryposis multiplex	1	–	1	1.1	0.333
Fetal akinesia syndrome	–	1	1	1.1	0.333
Pterygium syndrome	1	–	1	1.1	0.333
Larsen syndrome	–	1	1	1.1	0.333
Subtotal	7	6	13	13.7	4.329
Chromosomal aberration					
Down syndrome	2	2	4	4.2	1.333
Subtotal	2	2	4	4.2	1.333
Conjoined twins	1	–	1	1.1	0.333
Subtotal	1	–	1	1.1	0.333
More than one defect					
Prune-belly syndrome + cystic hygroma of neck	1	–	1	1.1	0.333
Cleft palate + talipes	1	1	2	2.1	0.666
Imperforate anus + ectopia vesicae + talipes + spina bifida	1	–	1	1.1	0.333
Subtotal	3	1	4	4.2	1.332
Miscellaneous					
Sacrococcygeal teratoma	1	–	1	1.1	0.333
Haemangioma	1	–	1	1.1	0.333
Hydrops fetalis	2	–	2	2.1	0.666
Neonatal teeth	1	1	2	2.1	0.666
Subtotal	5	1	6	6.3	1.998
Grand total	47	48	95	100	31.6

M – Male, F – Female

observations of Rasmussen et al. [*16*] and Refaat et al. [*17*]. The number of neonatal deaths was 18/3000 (0.6%) in the normal neonates and 14/95 (14.7%) in the malformed neonates, which confirms that malformations and genetic disorders are a major cause of neonatal death.

Sex was not found to have a role in the occurrence of congenital malformations, which concurs with the findings of Lei [*18*] (Table 1). Regarding birth order (Table 2), there was no significant relation between birth order and the prevalence of malformations. However, our study

Table 2 **Frequency distribution of birth order in the different groups studied**

Diagnosis	Birth order		
	1	2	≥ 3
Musculoskeletal	8	–	8
Central nervous system	8	3	10
Genital	5	–	3
Congenital heart diseases	2	1	–
Genetic syndromes	2	2	3
Miscellaneous	2	1	4
Cleft lip/palate	1	1	2
Chromosomal aberrations (Down syndrome)	2	1	1
More than one defect	1	2	–
Ear deformities	1		1
Imperforate anus	–	–	1
Total	32	11	33

Data could be obtained only in 76 cases

Table 3 **Distribution of affected cases according to parental consanguinity**

Diagnosis	No. with positive parental consanguinity/ total	%
Musculoskeletal	10/15	66.7
Central nervous system	10/23	43.5
Ear deformities	2/2	100
Imperforate anus	1/1	100
Genital	5/8	62.5
Congenital heart diseases	2/3	66.7
Cleft lip and/or palate	3/5	60.0
Genetic syndromes	7/10	70.0
Down syndrome	3/4	75.0
More than one defect	1/4	25.0
Miscellaneous	0/4	–
Conjoined twins	0/1	–
Total	44/80	55.0

Data could be obtained only in 80 cases
Consanguinity in all cases was 31.79%

showed that parental consanguinity was an important cause for most of the malformations (Table 3). Birth defects in the offspring of first-cousin parents was higher than in the offspring of non-consanguineous parents, which must be taken in account when counselling consanguineous couples.

From this study we emphasize that accurate and early diagnosis of congenital malformations is the key to proper management of cases. Premarital counselling is advised, especially in the presence of parental consanguinity and family history of a congenitally malformed child. Because of the high frequency of neural tube defects as revealed by our investigation, we recommend their proper prenatal diagnosis both by abdominal sonography and maternal serum α-fetoprotein at the population level. We also recommend providing periconceptional vitamins and folic acid to all pregnant women. Prenatal diagnosis for other malformations by ultrasonography at around 16 weeks of pregnancy should be a routine procedure. Cytogenetic prenatal diagnosis of Down syndrome and other chromosomal aberrations should be done in high-risk cases. We recommend that all neonates should be thoroughly examined and investigated for congenital malformations. An Egyptian registry of congenital malformations is needed.

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Hereditary disorders are an important problem because of the high number of consanguineous marriages in many countries of the Region. Haemoglobinopathies such as thalassaemia and sickle-cell disorders, and enzymopathies such as glucose-6-phosphate-dehydrogenase deficiency are commonly encountered. During 1997, the Regional Office made extensive efforts to support countries in assessing the extent of hereditary disorders and in identifying potential preventive strategies to be incorporated into national helath care systems. Technical support was also provided to some countries to strengthen their national congenital abnormality registries and neonatal screening systems.

Source: The Work of WHO in the Eastern Mediterranean Region. Annual Report of the Regional Director 1 January–31 December 1997, *page 145*