ORIGINAL ARTICLE

Risk factors of the appearance of anencephaly in Tunisia

Les facteurs de risque d'apparition de l'anencéphalie en Tunisie

Kaouther Nasri[1,2], Nadia Ben Jemaa[3], Soumeya Siala Gaigi[2]

1. Faculty of Sciences of Bizerte, University of Carthage, 7021 Zarzouna, Bizerte Tunisia.
2. Department of embryo-fetopathology, La Rabta Maternity and Neonatology Center, Tunis El Manar University, 1007 Tunis, Tunisia.
3. Department of histology-embryology, Faculty of Medicine of Tunis, Tunis El Manar University, Tunisia.

Abstract

Introduction: Anencephaly is a serious developmental defect of the central nervous system in which the brain and cranial vault are grossly malformed. The cerebrum and cerebellum are reduced or absent, but the hindbrain is present. Anencephaly is a part of the neural tube defect spectrum. This defect results when the neural tube fails to close during the third to fourth weeks of development, leading to fetal loss, stillbirth, or neonatal death.

Aim: To find out probable principal risk factors for the appearance of anencephaly.

Methods: This study was conducted to compare between pregnancies affected by anencephaly in 2002-2011 with those notified in the period 1991–2001. Statistical analysis was undertaken using chi-squared tests.

Results: Results had shown that anencephaly fetuses with a weight less than 1500 g were significantly higher in the period 2002-2011 than in 1991-2001 (P=0.003; OR= 4.32; CI= 1.62-11.53). Anencephaly cases aged more than 20 weeks of gestation (WG) were statistically elevated than cases aged less than 20 WG (P= 0.003). Maternal parity was associated with the appearance of anencephaly, where uni- or multiparous cases mothers were more likely to have an offspring with anencephaly than nulliparous mothers. Consanguinity presented a significant risk factor for the occurrence of anencephaly (P= 0.003). A logistic regression was run to examine the impact of several variables, only the maternal age was statistically significant.

Conclusion: This study clarified fields where efforts should be intensified, and surveillance data developed to prevent this malformation.

Key words: Anencephaly; Epidemiology; Feto-maternal characteristics; Risk factors; Tunisia.

Résumé

Introduction: L'anencéphalie est une anomalie grave du développement du système nerveux central dans laquelle le cerveau et la voûte crânienne sont gravement malformés. Le cerveau et le cervelet sont réduits ou absents, mais le cerveau postérieur est présent. L'anencéphalie fait partie du spectre des anomalies du tube neural. Ce défaut survient lorsque le tube neural ne se ferme pas au cours de la troisième à la quatrième semaine de développement, entraînant une perte fœtale, une mortinatalité ou un décès néonatal.

Objectif: Connaître les principaux facteurs de risque probables de l'apparition de l'anencéphalie.

Méthodes: Cette étude a été menée pour comparer les grossesses affectées par l'anencéphalie en 2002-2011 avec celles déclarées au cours de la période 1991-2001. L'analyse statistique a été réalisée à l'aide de tests du Chi carré.

Résultats: Les résultats ont montré que les fœtus anencéphaliques pesant moins de 1 500 g étaient significativement plus élevés au cours de la période 2002-2011 qu'en 1991-2001 (P=0,003; OR= 4,32; IC= 1,62-11,53). Les cas d'anencéphalie âgés de plus de 20 semaines de gestation étaient statistiquement plus élevés que les cas âgés de moins de 20 semaines de gestation (P = 0,003). La parité maternelle était associée à l'apparition de l'anencéphalie, les mères uni- ou multipares étant plus susceptibles d'avoir une progéniture anencéphalique que les mères nullipares. La consanguinité présentait un facteur de risque significatif de survenue d'anencéphalie (P = 0,003). Une régression logistique a été effectuée pour examiner l'impact des différentes variables étudiées, seul l'âge maternel était statistiquement significatif.

Conclusion: Cette étude a clarifié les domaines dans lesquels les efforts devraient être intensifiés et les données de surveillance développées pour prévenir cette malformation.

Mots clés: Anencéphalie; Épidémiologie; Caractéristiques fœto-maternelles; Facteurs de risque; Tunisie.

Correspondance
Kaouther Nasri
Department of embryo-fetopathology, La Rabta Maternity and Neonatology Center, El Manar II University, 1007 Tunis, Tunisia.
Email: nasrikaouther512@gmail.com

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Introduction

Neural tube defects (NTDs) result from a malfunction of neurulation caused by a very early interruption in brain and spinal cord development. It occurs around the 28th day after conception, when most women are not aware they are pregnant (1). Encephalocele, spina bifida and anencephaly are the three main forms of NTDs. In case of anencephaly, the normal development of the brain and the bones of the skull are prevented. Thus, the developing brain and spinal cord are exposed to the amniotic fluid that surrounds the fetus. This contact deteriorates the tissues of the nervous system, and thus the absence of large parts of the brain called cerebrum and cerebellum at birth. These regions of the brain are essential for thought, hearing, vision, emotions and the coordination of movements. Almost, babies with anencephaly die before birth or within hours or days after birth.

Multifactorial causes have been identified as disorders of embryonic neurulation (2): geographical conditions, race/ethnicity (2, 3), fetal sex (3, 4), high caffeine intake, low calorie diet, alcohol consumption (5), lack of folate supplementation at any time during pregnancy (3, 4, 5), use of oral contraceptives and passive smoking (6). Besides, other factors associated with NTDs comprise place of birth of mother, parity, timing of initiation of antenatal care, socioeconomic status (7), age of mother (4, 7) , education, nutritional status, drug use, presence of chronic maternal diseases, and severe infections during pregnancy (8).

The prevalence of anencephaly in Gorgan, northern Iran in the period (1998-2005) was 12/10,000 births (9), 104.4/10,000 in China (10), 0.5-0.6/1000 in Singapore (11), 0.01-7.42/10000 in Rijeka, Croatia (12), and 1.49/1000 in Santos Dumont (13).

In our previous study (2014) (14), we conducted an epidemiological study to determine the impact of certain feto-maternal characteristics in the appearance of all NTD subtypes over the period (1991-2011) in Tunisia. We found that the prevalence of NTDs during this period was 2.03/10000. And, one of the key findings was that there were numerous differences between the NTD subtypes, suggesting that there may be etiological differences between the subtypes. This implies that, although epidemiological studies usually do not make a distinction between NTD subtypes in studies, they should be analyzed one by one when possible.

Therefore, our present research sought to assess the differences in the distribution of cases of anencephaly according to feto-maternal characteristics and their evolution over time. Thus, to reveal the risk factors of the appearance of this anomaly and to detect the targets of intervention, a study was carried out by comparing the cases of pregnancy affected by anencephaly in the period (2002-2011) with those in the period (1991-2001).

Methods

Study design

A retrospective cross-sectional study was conducted to compare between pregnancies affected by anencephaly in 2002-2011 with those notified in the period 1991–2001.

Study setting and population

Tunisia is the northernmost country in Africa. It is a part of the Maghreb region of North Africa, and is bordered by Algeria to the west and southwest, Libya to the southeast, and the Mediterranean Sea to the north and east, covering 163,610 km2 (63,170 sq mi), with a population of 12 million.

The study was piloted in two periods: (1991–2001) and (2002-2011).

Data were collected from the Embryo-Fetopathology department of the Maternity and Neonatology Center of Tunis, Tunisia. Cases of anencephaly explored in this study concern all cases all over Tunisia and not only the cases of the capital (Tunis). This service assembles stillbirths and fetuses from all the other regional hospitals and private clinics as well as those from the center.

Analyzes in this study included malformed cases affected with anencephaly. Anencephaly cases associated with major birth defects were also included.

Variables

Using medical register, we recorded general informations about anencephalic stillbirths and their mothers: fetal sex, fetal weight, pregnancy outcome, maternal age, previous pregnancies and stillbirths, maternal blood type and consanguinity. To find a clear trend, the evolution of these cases was identified and analyzed by periods (1991-2001 and 2002-2011) by calculating the number of cases of anencephaly. We additionally calculated the prevalence of anencephaly cases and the sexes per 10,000 live births for each period, using annual birth statistics for Tunisians.

Data collection

The epidemiological study was carried out within the embryo-fetopathology department of the maternity and neonatology center of Tunis.

This service has a register in which children autopsied as part of a malformative assessment or as part of an etiological assessment are notified. The register contains all the informations concerning malformed babies and their mothers for each year since the opening of the center. The collected data were recorded in excel files used afterwards by the SPSS software for the statistical analyzes.

The prevalence of anencephaly cases and the sexes per 10,000 live births for each period were determined using annual birth statistics for Tunisians.

Data analysis

We assessed the differences in fetal/maternal characteristics of anencephaly cases in the two time periods (1991-2001 and 2002-2011), using chi-square tests by the statistical program SPSS v. 18. Differences in the distribution of fetal/maternal characteristics

were assessed by binary logistic regression. P< 0.05 was considered statistically significant. Odds ratios (OR) and their 95% confidence intervals (CI) were calculated to explore the probable association between maternal-fetal characteristics and the occurrence of cases of anencephaly.

Ethical consideration

Ethical approval for the study was obtained from the Ethics Committee of the Maternity and Neonatology Center in Tunis.

Results

During the period (1991-2001), 2,019,982 children were born in Tunisia. Among them, 81 cases of anencephaly were identified, giving an overall prevalence of 0.4 (± 0.18)/10,000 births. 1,783,907 births including 93 cases of anencephaly were observed during the period (2002-2011), i.e. an overall prevalence of 0.52 (± 0.18)/10,000. This increase was significant (P = 0.017).

The prevalence of females was equal to 0.47/10,000 (± 0.26) in (1991-2001) against 0.59/10,000 (± 0.29) in (2002-2011). The difference between females over the two periods was not significant (P = 0.35). For males, the prevalence was equal to 0.35/10,000 (± 0.23) in (1991-2001) against 0.46/10,000 (± 0.18) in (2002-2011). The difference between males over the two periods was significant (P = 0.025).

To study fetal characteristics, we analyzed: sex, weight and term (Table 1).

Gender comparisons were not significant between the two periods.

The median fetal weight was 825.33 g (± 863.41) with a minimum weight of 9.4 g and a maximum weight of 4100 g. In this current study, fetal weight was compared between two ranges (lower and higher than 1500 g). The results had shown that anencephalic stillbirths weighing less than 1500 g were four times more numerous over the period (2002-2011) than in (1991-2001) (P=0.003; OR= 4.32; CI= 1.62-11.53).

The median fetal term is 23.95 (± 7.37) weeks of gestation (WG) with a minimum term of 11 WG and a maximum of 40 WG.

We have found that stillbirths with anencephaly over 20 WG occurred twice as often in (2002-2011) (P=0.003, OR=2.59, CI=1.37-4, 89) and the termination of pregnancy was three times more frequent in the second period (p=0.001) (Table1).

To study the maternal characteristics, we analyzed: age, number of pregnancies, parity, consanguinity, drugs intake (Table 1) and blood group (Table 2). The average age of the mothers was 30.27 ± 5.37, with a minimum age of 19 years and a maximum age of 44 years. Maternal age over 30 had no significant impact on the occurrence of anencephaly (P= 0.61).

Maternal gravidity was not a risk factor for the occurrence of anencephaly (P= 0.38) (Table 1). However, maternal parity was significantly associated with this NTD subtype, where cases of uni- or multiparous mothers were more likely to have babies with anencephaly than nulliparous mothers. The results revealed that the cases of uni- or multiparous mothers were three times higher during the period (2002-2011) than in (1991-2001) (P= 0.01, OR= 3.5, CI= 1.31-9.32).

Table 1. Differences in distribution of maternal/fetal characteristics in cases with Anencephaly, Tunisia, 1991–2001 and 2002–2011.

Characteristics	1991-2001		2002-2011		P_{value}	OR	CI (95%)
	N	%	N	%			
Fetal sex					0.79	1.08	0.59-1.97
Male	45	56.2	51	54.3			
Female	14	43.8	29	45.7			
Fetal weight					**0.003**	**4.32**	**1.62-11.53**
≤1500g	61	77.2	88	93.6			
>1500g	18	22.8	6	6.8			
Fetal term					**0.003**	**2.59**	**1.37-4.89**
≤20	22	27.8	47	50			
>20	57	72.2	47	50			
Pregnancy outcome					**0.001**	**3.02**	**1.47-8.75**
FTD	3	3.8	0	0			
PB	6	7.6	0	0			
IUFD	45	57	19	20			
TOP	25	31.6	75	80			
Maternal age					0.61	0.83	0.41-1.67
≤30	32	58.2	43	53.8			
>30	23	41.8	37	46.2			
Gravidity					0.38	1.39	0.66-2.91
G=1	16	23.9	24	30.4			
G>1	51	76.1	55	69.6			
Parity					**0.01**	**3.5**	**1.31-9.32**
P=0	6	8.8	20	25.3			
P≥1	62	91.2	59	74.7			
Consanguinity					**0.003**	**3.44**	**1.53-7.71**
(+)*	26	56.5	17	27.4			
(-)**	20	43.5	45	72.6			
Medication intake (teratogenic drugs)	2	2.5	3	3.2	0.77	0.94	0.36-3.87
Positive triple test	5	6,3	20	21,3	**0.03**	**3.48**	**1,45-8.57**

To make statistical comparisons, 95% confidence intervals were reported by binary logistic regression.
The rates were considered statistically significant at the 5% level (P< 0.05).
The reference group is the period listed in column 2.
Results were not adjusted for additional potential confounders.
Fetal term was indicated per weeks of gestation.
G1= one gestation
G>1= multiple gestations
(+)*= consanguineous parents
(-)**= non consanguineous parents
FTD : full term delivery, PB : premature birth, IUFD: in utero fetal death, TOP: termination of pregnancy
Some data were missing.

Moreover, the association between consanguinity and the appearance of anencephaly was significant (P= 0.003, OR= 3.44, IC= 1.53-7.71). However, maternal blood group was not a risk factor as shown in Table 2 (P= 0.7).

A logistic regression was run to examine the impact of several variables on the appearance of anencephaly, only maternal age was statistically significant with p=0.013.

Table 2. Differences in distribution of blood type in mothers with anencephaly-affected pregnancies, Tunisia, 1991–2001 and 2002–2011.

Maternal blood type	1991-2001		2002-2011		P value
	N	%	N	%	
O+	21	48.8	28	44.4	
A+	11	25.6	18	28.6	
B+	5	11.6	7	11.1	
AB+	0	0	2	3.2	0.7
O-	5	11.6	4	6.3	
A-	0	0	2	3.2	
B-	1	2.3	2	3.2	
AB-	0	0	0	0	

The rates were considered statistically significant at the 5% level (P< 0.05).
Some data were missing.

Discussion

In this study, a significant increase in the prevalence of stillbirths with anencephaly was observed over both periods (1991-2001/2002-2011) (from 0.40 to 0.52/10,000) (P = 0.017).

The small number of cases in this current study is due to the fact that this anomaly is rare in our country.

In contrast, there was a regression of anencephaly after the introduction of the fortification program in South Africa (15), the United States and Canada (16). The prevalence also declined in Singapore (11), from 0.54/1000 in 1993 to 0.32/1000 in 2002. Significant declines in anencephaly were observed among Hispanic births and non-Hispanic white births after fortress (17).

Berg (2003) (18), pointed out that the highest rates of cases of anencephaly occur in Great Britain and Ireland, and the lowest incidence rates occur in Asia and Latin America.

In Iraq, anencephaly is the most common neural tube defect (19). Benjelloun et al. (1983) (20) reported a high prevalence of anencephaly in Morocco, particularly in post-maturity males.

Some studies have shown that the sex of the fetus is a risk factor for a rise in this NTD subtype. They showed that females are more likely to have anencephaly than males (21,22-23). According to WuY et al. (1995) (23), the sex ratio for NTDs is 0.59, with prevalence in female infants (32.1 per 10,000) compared to males (17.4 per 10,000).

In our study, an increase in the prevalence of each sex was observed over both periods but the difference was significant only for male.

In China, the prevalence of males with anencephaly was 966.2/10,000, which was significantly higher than the prevalence of cases in females (2002-2004) (10). In Singapore, the F:M sex ratio was 7:10 in (1993-2002) (11), however in Iran it was 29:27 over the period 1998-2005 (9). In Rijeka, Croatia it was 5:2 (12) and 4:1 in Brazil (13).

To analyze fetal characteristics, we studied: sex, weight and fetal term.

Gender comparisons are not significant between the two time periods (Table 1). This result is in contradiction of the results of other studies which have inferred that females are more likely to have anencephaly than males (3, 4, 6, 24, 25-26). However, the analysis by Obeidi et al (2010) did not show this predominance (27).

In the literature, no explanation has been found for this predominance of females in anencephalic fetuses. This could be the subject of further studies.

The results had shown that anencephaly stillbirths with a weight of less than 1500 g were significantly higher than those with a weight of more than 1500 g.

Indeed, according to the observations made in our fetopathology center, a fetus with anencephaly weighs less than a normal fetus since its organs do not develop normally such as the cranium, the brain, the meninges, etc. ...

Especially during embryo-fetal development, the brain is large because it contains all the capital of neurons. At the 10th week, it represents the 10th of the total weight of the embryo, and at birth, it represents the 5th of the total weight of the body. In our population of malformed children, the brain is lacking in case of anencephaly (28).

Anencephaly stillbirths over 20 WG were statistically the highest in our population with a higher rate of TOP. Similarly, the same result was obtained in our previous study concerning spina bifida (29).

Additionally, Saad et al (30) observed that the highest risk of stillbirth among non-Hispanic blacks was primarily stroked before 24 WG. Willinger et al (31) approved this consideration where the greatest black-white disparity in the risk of stillbirth in ongoing pregnancies is between 20 and 23 WG.

In order to study maternal data, we analyzed: age, number of pregnancies, parity, consanguinity, blood group and.

Parity was significantly associated with an increased risk of developing anencephaly in fetuses. In fact, the results revealed that the cases of uni- or multiparous mothers were three times higher over the period (2002-2011) than in (1991-2001) (P = 0.01, OR = 3.5, CI = 1.31-9.32). Our data were consistent with several previous reports (9, 24). However, this result contradicts the research of Berg (2003) (18) who found that parity was not a risk factor for the occurrence of anencephaly in Great Britain.

Indeed, the risk of having a malformed child is increased at the age of 30 years of the mother and becomes more important after the age of 35 years. This is mainly due to the aging of gametes, mostly female. This hypothesis is based on the fact that oogenesis begins with a very long meiotic prophase and that oocytes produced at the end of reproductive life show a higher proportion of chromosomal abnormalities (32).

In addition, advanced age associated with multiparity may increase the risk of maternal vitamin deficiency (33). This deficiency is an important factor that could lead to an increased risk of having a malformed baby in subsequent pregnancies (33).

In this current study, inbreeding was also associated with anencephaly (P = 0.003) (Table 1). However, according to Berg (18), no known correlation of the occurrence of anencephaly in inbred mating has been verified, nor any relationship of heredity revealed.

No associations were found for maternal age, gravidity, and maternal blood group among the outcome groups, showing that these were not risk factors associated with

anencephaly.
In contrast, maternal age was a risk factor in some studies where the highest rate of anencephaly was 13.1/10,000 in babies born to mothers over the age of 35 in Iran (9). But the highest rate was observed among women aged 20 to 29 in Brazil (19/10,000) (24).
Moreover, increasing gravidity, high or low age of mothers during pregnancy were found as maternal factors significantly associated with increased risk of anencephaly in Iran (9).
In addition, having less than three pregnancies has been considered a risk factor for anencephaly in a sample of affected live newborns (34).
In our study, a logistic regression was run to examine the impact of several variables, only the maternal age was statistically significant, teratogen drugs intake and some other data were missing from medical records.

Conclusion

To uncover possible underlying causes for the onset of anencephaly and identify targets for intervention, a survey was undertaken comparing pregnancy notifications affected by anencephaly over the period (2002-2011) with notifications during the period (1991-2001). The increase in this study was significant so this must be taken into consideration to make essential preventions in order to reduce the occurrence of this malformation.
The results presented here could contribute to a better understanding of the outcome of pregnancies affected by this fatal malformation, allowing obstetricians a more detailed discussion with the families concerned about fetal and maternal complications, associated conditions and prognosis of fetuses with a prenatal diagnosis of anencephaly.
However, these results cannot fully explain the observed increase in anencephaly reports and suggest that future epidemiological studies should consider additional comparisons to assess these subtypes.

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