



## Prevalence and Factors Associated at Presence of Central Nervous System Congenital Malformations

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### Authors' contributions

This work was carried out in collaboration between all authors. Author RP designed the study, wrote the protocol, and wrote the first draft of the manuscript. Authors FPR and CCCO managed the analyses of the study. Author EVM performed the statistical analysis. Author JAA co-designed the study, managed the literature search and proof read the first draft manuscript. All authors read and approved the final manuscript.

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### ABSTRACT

**Introduction:** Congenital malformations are currently an important cause of morbidity and mortality in many countries, though in most cases their etiology is unknown. The central nervous system (CNS) is involved in many of these defects.

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**Objective:** To study the factors associated with CNS congenital malformations and their prevalence in infants born at a high risk maternity hospital in Northeastern Brazil.

**Materials and Methods:** A case-control study performed from January 2010 to December 2011, with data from The Latin American Collaborative Study of Congenital Malformations.

**Results:** Among the 8.405 registered births, 187 were malformed newborns (2.2%). Nervous system malformations were diagnosed in 61 patients (32.6% (CI = 95% 27.5 to 38.0)), the most frequent being neural tube defects and congenital hydrocephaly. Previous history of miscarriage and/or stillbirth ( $p = 0.008$ ), family history of malformations ( $p < 0.001$ ) and parental consanguinity ( $p = 0.028$ ) are associated with CNS malformation. Environmental factors such as maternal chronic diseases, smoking, exposure to teratogenic drugs and alcohol presented no statistically significant differences.

**Conclusions:** The genetic component was an important contributing factor to the etiology of the malformations studied.

*Keywords: Birth defects; Central nervous system malformations; neural tube defects; risk factors.*

## 1. INTRODUCTION

Congenital malformations (CM) are defined as any functional or structural defect occurring during the development of the fetus due to genetic, environmental or unknown factors that may have origin before birth, whether they are apparent in the newborn or they only become apparent later on [1]. CM affect approximately 3% of newborns and cause about 20% of deaths during the neonatal period [2]. For over 20 years, CM have been the leading cause of infant mortality in the United States and, since 2000, the second most common cause in the majority of Latin American countries [2]. Approximately 13% of CM involve the central nervous system (CNS). After congenital heart defects, this is one of the most common congenital deficiencies [3-5]. Neural tube defects (NTDs) are CNS malformations due to deformities in the neural tube dorsal midline structures, which are one of the most frequently occurring types of CNS malformation, with a worldwide incidence among 1.0 to 10.0 cases for every 1.000 births, with most cases categorized as anencephaly and spine bifida [6].

The etiology of about 70% of the CM remains unknown [5]. Epidemiological and experimental studies conducted over the past decades have demonstrated the importance of the interaction between genetic and environmental factors as a possible basis of the etiology of such malformations [4]. Maternal smoking, inadequate nutrient ingestion, maternal fever, infections, diabetes, anticonvulsants, toxic environmental agents - such as metals, pesticides and nitrate - represent some possible environmental factors involved in the genesis of some CM [2,5].

The impact caused by the birth of a malformed fetus is not restricted to morbidity and mortality. The CM is responsible for the loss of a high proportion of potential years of life, numerous hospitalizations and high medical costs; added to these factors the psychosocial effects which involve the entire family [1].

The acquisition of new knowledge and new diagnostic techniques - as well as epidemiological, genetic and teratology studies - have provided great advances in the field of reproductive biology to determine various causes responsible for developmental abnormalities and, therefore, the discovery of various preventative methods [7]. Thus, the characterization and epidemiological investigation of possible factors associated with CM become crucial for the development of preventative strategies that have an impact on the incidence of these malformations [2].

The European Surveillance of Congenital Anomalies (EUROCAT) and the National Birth Defects Prevention Study (NBDPS) are population-based epidemiological congenital defects surveillance programs, operating in Europe and in the United States, respectively [8,9]. In South America, the Latin American Collaborative Study of Congenital Malformations (ECLAMC) acts as a clinical and epidemiological research program, analysing risk factors involved in the etiology of CM by means of a hospital based case-control study [10].

The present study describes the prevalence, the clinical presentation and the factors associated with CNS malformations in newborns (NB) at an ECLAMC-participating high risk maternity hospital in Northeastern Brazil.

## 2. MATERIALS AND METHODS

An observational, case-control, cross-sectional and analytic study held at Nossa Senhora de Lourdes Maternity, located in the city of Aracaju. It is a referral hospital for high-risk pregnancies in Sergipe, which also attends patients with high risk pregnancies from other Northeastern States of Brazil, such as Bahia, Alagoas and Pernambuco.

In order to carry out this study, the database of Nossa Senhora de Lourdes Maternity, which contains the ECLAMC records involving all births that have occurred between January 2010 and December 2011, was used. NB who had clinical and/or ultrasound CM of the CNS, and their respective controls, were included in the study.

The ECLAMC defines its criteria as all malformed NB, dead or alive, with 500 g or more, born in the participant maternity, from its date of entry in the program. The newborn control group is made up of infants born alive, not malformed, of the same sex as, and born immediately after, the malformed infant.

The occurrence of the CM of the CNS (considered as an outcome variable) was stratified according to embryogenesis into: NTDs (anencephaly, meningocele, myelomeningocele, encephalocele), CNS midline defects (holoprosencephaly, agenesis of the corpus callosum or of the septum pellucidum, arrhinencephaly) malformations of the brain stem and cerebellum (Arnold Chiari and Dandy-Walker malformation), failures in the neurogenesis (macrocephaly, microcephaly, micropolygyria) and congenital hydrocephalus [11].

The evaluated variables included gender, birth weight, gestational age, age, parents' level of formal education, parents' occupation, parental consanguinity, history of miscarriage and/or stillbirth, parity, type of pregnancy, mode of delivery, prenatal data (prenatal queries, prenatal complications, maternal diseases, use of medications and illicit drugs), age at diagnosis (prenatal, natal or postnatal) and type of evidence for the diagnosis (clinical and/or ultrasound).

The ECLAMC record information was tabulated using SPSS software (Statistical Package for Social Sciences). For categorical variables simple frequencies were calculated with scores and percentages with their respective confidence

intervals for 95%, when necessary. For quantitative, average and standard deviations or medians and percentile, 25 and 75, were calculated when appropriate. The bivariate analysis included the chi-square or Fisher exact test to assess the association between categorical variables expressed and the occurrence of CNS malformation. Similarly, for the association between the outcome and the quantitative variables, the Student or Mann-Whitney t-test was used. Verifying the association between congenital anomaly and the risk factors, the estimated odds ratio by multivariate logistic regression was calculated. It was considered as the significance level  $p \leq 0.05$  and the two-tailed tests of hypotheses.

The project was approved under the protocol number 141012 by the Tiradentes University Ethics Committee.

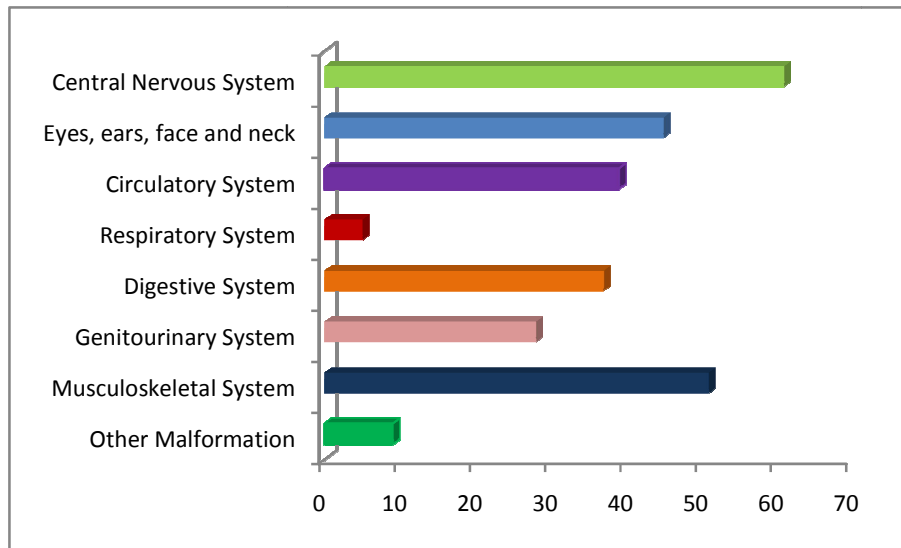
## 3. RESULTS

There were 8,405 births between January 2010 and December 2011. Among these, 187 NB had some CM. Of these, 61 cases (32.6%) were diagnosed with CNS malformations (CI = 95%, 27.5 - 38.0) (Fig. 1).

The distribution of CNS malformations classified according to embryogenesis is shown in Table 1. Among the NTDs, cases of myelomeningocele, encephalocele and anencephaly had similar frequencies; in only one case was there an association between myelomeningocele and anencephaly. One case of myelocele was described.

The sociodemographic characteristics of the parents in the study group and those of the control group are shown in Table 2. The level of education and occupation of both mother and father were equally distributed in both groups. Most mothers and fathers had not completed the first grade (basic education). In terms of occupation, most of the mothers were housewives, while the fathers were unskilled laborers.

Table 3 presents the characteristics related to pregnancy and NB. The median of antenatal consultations was 6 [5,8] for malformed fetuses and 7 (5,8) for the control group, with no statistically significant difference between groups ( $p = 0.85$ ).



**Fig. 1. Distribution of Congenital Malformations according to the affected system. \*in the same fetus, there may be more than one affected system**

**Table 1. Distribution of categories of Congenital Malformations of the Central Nervous System, according to embryonic development, occurring in neonates (n =61) attended at the Nossa Senhora de Lourdes Maternity, Aracaju/SE, between 2010 and 2011**

Congenital malformation of the central nervous system	n (%)61	CI 95%
NTDs	25 (41.0)	29.5 - 50.8
Myelomeningocele <sup>a</sup>	8 (13.1)	
Encephalocele <sup>a</sup>	7 (11.5)	
Anencephaly <sup>a</sup>	8 (13.1)	
Others <sup>a</sup>	2 (3.3)	
CNS MD	7 (11.5)	4.9 - 11.5
MBSC	6 (9.8)	3.3 - 14.8
FN	8 (13.0)	4.9 - 19.7
CHydrocephalus	26 (42.6)	29.5 - 52.5

NTDs = Neural Tube Defects; CNS MD = Central Nervous System Midline Defects MBSC = Malformations of the Brain Stem and Cerebellum; FN = Failure in Neurogenesis; CHydrocephalus = Congenital Hydrocephalus, CI 95% = Confidence Interval of 95% \* patients may have more than one diagnosis in common <sup>a</sup>because of the small number of the sample, the confidence interval was not calculated

**Table 2. Socio demographic variables of children’s parents with Congenital Malformations of the Central Nervous System and the control group attended at Nossa Senhora de Lourdes Maternity, Aracaju/SE, between 2010 and 2011**

Sociodemographic variables	Study n <sup>2</sup> =61n (%)	Control n <sup>2</sup> =61n (%)	p*
Maternal Age <sup>1</sup>	26.8 ± 7.3	26.1 ± 7.7	0.59
<b>Maternal Age (years)<sup>#</sup></b>			<b>0.84</b>
< 20	12 (19.7)	14 (23.3)	
≥ 20 < 35	38 (62.3)	37 (61.7)	
≥ 35	11 (18.0)	9 (15.0)	
Paternal Age <sup>1</sup>	31.5 ± 9.3	29.7 ± 7.8	0.23
Parental Consanguinity	7 (11.5)	1 (1.6)	0.028

<sup>1</sup>Age in years expressed as average and standard deviation, Student’s t-test; other chi-square tests <sup>2</sup>n= number of cases <sup>#</sup>one patient in the control group had no record of age \*comparison between the fetuses group with congenital malformation of the Central Nervous System (study) and the control group.

**Table 3. Variables related to pregnancy and fetuses with Congenital Malformations of the Central Nervous System and the control group, attended at Nossa Senhora de Lourdes Maternity, Aracaju/SE, between 2010 and 2011 features**

<b>Variables of pregnancy and fetuses</b>	<b>Study n=61n (%)</b>	<b>Control n=61n (%)</b>	<b>P</b>
Gestational Age <sup>1</sup>	36.1 (3.2)	37.3 (2.7)	0.027
<b>Gestational age</b>			0.18
<37 weeks	26 (42.6)	19 (31.1)	
37 - 41 weeks	35 (57.4)	42 (68.9)	
Weight <sup>2</sup>	2.624,7 (975.4)	2.888,4 (785.4)	0.10
<b>Categorized weight (grams)</b>			0.24
<2.500	25 (41.0)	18 (29.5)	
2.500-3.500	23(37.7)	32 (52.5)	
>3.500	13 (21.3)	11 (18.0)	
Previous History of MC/SB	9 (14.8)	1 (1.6)	0.008
Family history of MF	23 (37.7)	5 (8.2)	<0.0001
AHDP	9 (14.8)	24 (39.3)	0.002

<sup>1</sup>Gestational Age expressed in weeks as average and standard deviation; <sup>2</sup>Weight expressed in grams as average and standard deviation; MC=Miscarriage; Stillbirth=SB; MF=Malformed; AHDP= Acute Hypertensive Disorders of Pregnancy.

Among the 61 pregnant patients with malformed fetuses, 59 underwent gestational ultrasound (GUS) during the prenatal period and of these, 48 (78.7% CI = 95% 67.8 - 87.9) had a diagnosis of malformation over that period. The diagnosis was made after 24 hours of life in 13.1% of infants (CI =95 % 5.6 - 21.8) while the others had received their diagnosis at birth.

The most frequent comorbidities were acute hypertensive disorders of pregnancy, followed by urinary tract infection. Maternal chronic diseases such as diabetes, epilepsy, asthma and hypothyroidism did not present statistically significant differences between the two groups. Haemorrhage, illicit drug use, smoking and drinking alcohol during pregnancy also presented no statistically significant differences between groups.

The use of folic acid in the preconception period was only observed in one patient from the control group, and was not reported even in mothers with a history of familial congenital malformation. Regarding the use of folic acid in the first trimester of pregnancy, there was no statistically significant difference between mothers with malformed fetuses and the control group (p = 0.28). Cesarean section was the most frequent mode of delivery in both groups, with rates of 73,8% and 68,9%, respectively (p = 0.45). Multiple pregnancy occurred in only 3% of cases of malformed and in 2% of the control group (p = 0.64). Cephalic presentation was the position most frequently observed, with a lower incidence in the malformed NB group compared to the

control group (86.9% and 93.5%) (p = 0.18). The average birth weight of the malformed group was 2624.7g; there was no statistically significant weight difference between this and the control group (2888.4g) (p = 0.10).

32 cases of malformations of other organs or systems, which corresponded to 52.5% of fetuses with CNS malformations (CI = 95% 39.3 - 64.5) were found. The malformations of eye, ear, face and neck, which included the cleft lips and palates, were those most commonly associated with CNS congenital malformations, present in 59.4% (CI = 95% 40.6 - 68.8) cases, followed by malformations of the musculoskeletal system (50.0% CI =95 % 33.3 - 66.7) and by malformations of the circulatory system (34.4 % CI = 95% 18.2 - 50.0).

Gestational age, parental consanguinity, a family history of malformations, miscarriage and/or stillbirth history and the presence of acute hypertensive disorders of pregnancy were statistically significant variables, subjected to logistic regression, taking the presence of CNS congenital malformations as a dependent variable. Initially, the unadjusted odds ratios for the associated factors described above were calculated and, subsequently, with the adjusted odds ratios, risk factors for the presence of CNS CM parental consanguinity, family malformed and stillborn and/or previous abortion history were taken into consideration (Table 4). Among the seven cases of CNS MF with a history of parental consanguinity, NTDs were present in three cases, two of which were diagnosed as

encephalocele and the other as myelomeningocele. Congenital hydrocephalus was described alone in one case and in two, it was associated with holoprosencephaly and encephalocele. Malformations of the brain stem and cerebellum were reported in two cases.

#### 4. DISCUSSION

In the present study, the overall rate of birth defects in the population in this research was of 2.2% (CI = 95% 1.9 - 2.4). This discovery is similar to those described in other studies, which show variable rates between 1.4 % and 4.2% [10]. The CNS malformations present in 32.6% of malformed NB were those most frequently observed. Data from the European study demonstrate that cardiac defects are the most common subgroup of non-chromosomal CM, followed by limb defects, abnormalities of the urinary system and nervous system defects; the latter contributes with 2.3 cases per thousand births [12]. However, in other studies, the CNS malformations are described as the most common CM, with rates similar to those found in this research [13,14].

There is the possibility that differences in study populations, as well as in representation and diagnostic methodology used, can underdiagnose small defects, especially those of the heart. A greater number of congenital heart diseases could be diagnosed by routine echocardiogram. However, this is not common practice [15].

The NTDs are part of a group of CM regarded as serious, which affect about one in every thousand pregnancies, most commonly represented by anencephaly and myelomeningocele [16]. The prevalence of NTDs found in this study was 30 in 10.000 pregnancies (CI = 95% 19.0 - 44.0), which is similar to that described in other studies [6,16]. Anencephaly and myelomeningocele were the most commonly found NTDs in the population studied, both with similar frequencies, as demonstrated in the bibliographic reference [2,6,10].

Encephalocele is also part of the spectrum of NTDs and consists of a herniation through bone defects, whose content may include cerebrospinal fluid, meningeal structures or brain tissue, usually covered by intact skin and located in the occipital region [17]. In this study, the prevalence was of 8.3 cases per 10.000 births. This rate was higher than rates reported in other

studies, from 1.0 to 4.0 cases per 10.000 births [17], and described by ECLAMC (2.1/10.000 births) [10].

Although an important decrease of cases of NTDs has been registered since the implementation of fortification of flour and folic acid supplementation in women of childbearing age, they still constitute the most important malformation of CNS [18,4]. The genetic component seems to represent the greatest risk factor for the occurrence of NTDs, and the genes that regulate the folate metabolism have been strongly implicated [16]. Studies describe some cases of NTDs that do not respond to supplementation with folic acid, assuming that there may be a subpopulation with a poorer response to this supplementation, which would be determined by genetic factors [4]. No pregnant women with malformed fetuses, including those with a previous history of malformation, made use of folic acid supplementation in the preconception period, and only 32% of the women included in the study were treated in the first trimester of pregnancy.

Congenital hydrocephalus has been reported as having an overall prevalence of 4.65 cases per 10,000 births [19] and it is characterized by a disturbance of cerebrospinal fluid circulation, with intraventricular accumulation of cerebrospinal fluid, which results in progressive ventricular dilatation, which may clinically present as isolated or associated with other congenital defects [20,21]. In Brazil, the reported rate is 22.3 cases per 10.000 births, considered significantly higher than in other Latin American countries [10]. The prevalence found in this study was 31 per 10.000 births (CI = 95% 20.0 - 44.0), which was far higher than the rate found in other research [18,10,2]. However, it was similar to that one found in a fetal medicine reference service in Southeastern Brazil [20]. This discovery may be related to the fact that the study was performed in a referral hospital for high-risk pregnancy, to where women at high risk, including those with a diagnosis of CM are directed. In 38.5% of cases the hydrocephalus was associated with other CM of the CNS, which was a similar finding to that described in another study [21].

An appropriate diagnostic approach is essential to properly identify the CM, optimizing intervention strategies, among which the referral to tertiary care centres, the definition of time and mode of delivery, anticipating care

**Table 4. Odds ratio adjusted for factors associated with congenital malformations of the central nervous system, occurring in neonates (n =61), attended at Nossa Senhora de Lourdes Maternity, Aracaju/SE, during the period 2010 to 2011**

Variable	Oddsratio	CI 95%	P
<b>Parental consanguinity</b>			
Yes	12.81	1.48 – 111.0	0.021
No	1		
<b>Previous history of MC/SB</b>			
Yes	13.39	1.56 – 114.43	0.018
No	1		
<b>Family history MF</b>			
Yes	8.08	2.73 – 23.89	< 0.0001
No	1		

*Method: exact logistic regression; MC=Miscarriage; SB = Stillbirth; MF=Malformed; CI 95%= Confidence Interval 95%*

subspecialties, as well as conducting family counseling regarding prognosis and therapeutic management [9]. Diagnostic imaging methods, especially transvaginal and high-resolution three-dimensional ultrasound, as well as magnetic resonance imaging, have been an important tool in prenatal assessment of CNS malformations, allowing increasingly accurate diagnoses [22]. In this analysis, it was noted that 98.4% of all the pregnant women had access to ultrasonography in the prenatal diagnosis of malformation, and that it was performed in 78.7% cases of malformed fetuses, a higher rate than that found in a previous academic study [9].

The CM can be presented as single or multiple, and the fetuses with malformations can be classified among those with recognizable conditions, chromosomal or non-chromosomal and those without recognizable conditions [23]. Research papers report that about 40% of cases of CNS malformations are associated with other congenital defects [3]. Among fetuses with NTDs, there are reports that confirm that 20.4% had other associated malformations, the most commonly found being cleft lip and palate, musculoskeletal, cardiovascular and renal malformations [23]. The present study showed higher rates than those reported in other studies [3]. These discoveries suggest the need for a comprehensive diagnostic investigation into the occurrence of other abnormalities in children with CNS malformations.

Parental consanguinity, previous history of miscarriage and/or stillbirth and previous cases of malformation in the family were the only factors independently associated with CNS malformations, according to the multivariate analysis. Parental consanguinity is a recognized

risk factor for the occurrence of congenital malformations, such as hydrocephalus, postaxial polydactyly of the hands and cleft lip and palate [24]. Miscarriages occur in about 15% of such pregnancies. Although about 50% of cases have no clear etiology, academic studies report genetic factors as the main cause of miscarriage [25]. Family history of CM is also described as a factor associated with the presence of CM, derived from 16.7% of cases [14], which represents a lower frequency than that found for CNS malformations in the present study.

Environmental factors have often been described in academic research papers as single or associated determinants along with a genetic component in the genesis of many CM [2,5]. Some characteristics of the parents such as age, education and presence of chronic maternal conditions, such as diabetes, are some of these factors [6,14,26]. Statistically, these factors are not significant in the study. Nor were maternal smoking [27], illicit drug use [28] or alcohol consumption during pregnancy [29] statistically significant in the presence of CNS and CM].

One limitation of our study is the sample size. A sample covering a larger number of births could infer other factors, especially environmental factors as being important determinants in the genesis of CM of the CNS.

## 5. CONCLUSION

According to the findings, it can be inferred that a genetic component is an important factor in the etiology of the malformations studied, demonstrated by the association of these defects with parental consanguinity and a family history of malformation and spontaneous abortion and/or stillbirth.

## CONSENT

All authors declare that written informed consent was obtained from the parents of the patient for publication of this study.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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