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NEUROLOGICAL CONGENITAL MALFORMATIONS IN A TERTIARY HOSPITAL IN SOUTH BRAZIL

Ana Guardiola[1,2], Vanessa Koltermann[1], Paula Musa Aguiar[1], Sérgio Pilla Grossi[1,2], Valéria Fleck[3] , Elisabeth C. Pereira[3] , Lúcia Pellanda[1,4]

Abstract – **Background:** Congenital anomalies are one of the main causes of morbidity and mortality among infants. The involvement of the central nervous system (CNS) occurs in 21% of cases. **Objective:** To identify incidence of CNS malformations and associated factors in newborns at a Terciary Hospital of Porto Alegre. **Method:** Case-control study conducted between 2000 and 2005 based on the Latin American Collaborative Study of Congenital Malformations database. **Results:** Among 26,588 births registered in this period, 3.67% presented with malformations (IC=95%; 3.44–3.9), being 0.36% of the CNS (IC=95%,(0.29–0.43)). The most common CNS malformation was meningomielocele (10.4%). Young maternal age (p=0.005); low birth weight (p=0.015); large cephalic perimeter (p=0.003); post term birth (p=0.000) and low APGAR indexes at the 1st and 5th minutes were associated with CNS malformations. **Conclusion:** We found an incidence of CNS malformations similar as compared to literature.

KEY WORDS: neurological malformations, neural tube defects, risk factors, congenital malformations.

Malformações neurológicas congênitas observadas em hopsital terciário no sul do Brasil

Resumo – Anomalias congênitas são umas das principais causas de morbimortalidade infantil. O sistema nervoso central (SNC) é acometido em 21% dos casos. **Objetivo:** Identificar a incidência e fatores associados a malformações do SNC em recém nascidos na maternidade de um hospital terciário de Porto Alegre. **Método:** Estudo controle realizado de janeiro de 2000 a dezembro de 2005, baseado no banco de dados do Estudo Colaborativo Latino Americano de Malformações Congênitas. **Resultados:** Dos 26.588 nascimentos, 3,67% apresentaram malformação (IC=95%; 3,44–3,9), com 0,36% do SNC (IC=95%, (0,29–0,43)). A malformação do SNC mais comum foi hidrocefalia (10,9%). Menor idade materna (p=0,005); menor peso ao nascimento (p=0,015), maior perímetro cefálico (p=0,003); nascimentos pré-termo (p=0,000) e menores índice APGAR no 1° e 5° minutos (p<0,000) apresentaram associação com malformações do SNC. **Conclusão:** Foi encontrada incidência similar de malformações do SNC comparada à literatura.

PALAVRAS-CHAVE: malformações neurológicas, defeitos tubo neural, pé torto, fatores de risco.

Congenital malformations develop during intrauterine life and, therefore, are present at birth, although they may be unrecognized at that moment. Neural tube defects (NTDs) occur due to embryonic neural tube closure failure during the fourth week of embryogenesis[1]. Congenital anomalies cause a significant proportion of embryonic and fetal deaths, and stand among the leading causes of infant mortality and morbidity, affecting 2–5% of all newborns and contributing significantly for mortality at the age of one year[2,3]. Approximately 21% of these anomalies involve the central nervous system (CNS), constituting one of the commonest birth defects, second only to heart defects[4]. Recent *in vitro* and *in vivo* studies have detailed the molecular mechanisms of neurulation in vertebrates. Nevertheless, the morphologic development of the human neural tube is still poorly understood[5]. The term "Neural tube defect" may be used to refer to any spinal or cerebral malformation. NTDs constitute a heterogeneous and complex group of congenital anomalies, and may occur alone or in combination with many other

[1]Federal University Foundation of Porto Alegre (UFCSPA), Porto Alegre RS, Brazil; [2]Irmandade Santa Casa de Misericórdia, Porto Alegre RS, Brazil; [3]ECLAMC (Latin American Collaborative Study of Congenital Malformations), Porto Alegre RS, Brazil; [4]University Foundation of Cardiology (FUC), Porto Alegre RS, Brazil.

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Dra. Ana Guardiola – Sarmento Leite 245 - 90050-170 Porto Alegre RS - Brasil. E-mail: guardiola@cpovo.net

neurological or non-neurological defects. Most isolated NTDs have a multifactorial origin[5]. Despite the fact that NTDs do not follow a Mendelian pattern of inheritance, this defects show strong familiar clustering, possibily indicating a genetic etiology. Risk of recurrence in siblings of meningomyelocele patients is about 2–5%[6]. The incidence of NTDs among first and second degree relatives is somewhat higher than for non-selected populations. Case reports and epidemiological studies have implicated a series of agents in the etiology of NTDs, including chemical products, solvents, abuse substances, drugs, pollutants and infectious diseases. Additionally, maternal hyperthermia, valproate use, nutritional inadequacies and chronic disease, such as diabetes mellitus, have been associated to an elevated incidence of NTDs, as well as socio-economic variables and parents occupation[7,8].

A recent metanalysis including 33 studies suggests that there is association between maternal age and certain types of NTDs. This association could be stronger with spina bifida than with anencephaly[9]. It is well known, nonetheless, that periconceptional daily supplementation with folic acid is effective in reducing the incidence of NTDs[10]. There is considerable variation in the reported incidence of congenital malformations in different populations, ranging from 1.07% in Japan to 45.2% in Egypt[2]. Seasonal, ethnic and geographic factors may be implicated[1,2]. Incidence has been reported to decrease in some areas, while in others it has been held constant[2]. Although the reasons for this decrease are still unknown, improvement of prenatal diagnosis, selective pregnancy termination, genetic counseling and, possibly, folic acid supplementation could be implicated[11]. Facing the high incidence and prevalence of congenital malformations, with significant costs to society and the severe impact that birth defects represent for individuals and families, detailed investigation of these conditions is of paramount importance in planning effective prevention strategies.

In South America, the Latin American Collaborative Study of Congenital Malformations (ECLAMC) is a case-control study that aims to investigate clinical and epidemiological variables of newborns with congenital anomalies, including risk factors.

The present study was undertaken in a tertiary reference center in south Brazil, participating in ECLAMC since 1990. We sought to describe the incidence, clinical presentation and risk factors of CNS malformations in this setting.

METHOD

ECLAMC is a case-control study of congenital malformations, and its methods have been described elsewhere[12]. For the present study, we analyzed the ECLAMC database at Complexo Hospitalar Santa Casa, Porto Alegre, Brazil, including all births from January, 2000 to December, 2005. All newborns and stillbirths with neurological congenital malformations were identified.

Cases were defined as any clinically detectable morphological abnormality in any pre or post gestational age. All live birth cases were paired with a control. The first newborn of the same gender and with no malformations, being born in the same hospital immediately after the case was included as the paired control.

Variables evaluated included gender, birth weight, gestational age, APGAR scores in the first and fifth minutes, presence of associated congenial malformations, parental consanguinity, multiple pregnancy, maternal age, type of delivery, pregnancy information (prenatal follow up visits, intercurrences, maternal diseases, medications, substance abuse), newborn clinical status, amniotic fluid aspect and socioeconomic data.

All statistical analyses were performed with the aid of SPSS software. Continuous data is described as means ± one standard deviation, and categorical data as proportions. Chi square and Students' t test were used to compare groups. Odds ratios and 95% confidence interval were estimated. Multivariable logistic regression models were used to study the association of risk factors and malformations. The analyses were considered significant if $p<0.05$.

The study was submitted for evaluation by the Ethics and Research Commission of this institution where the study was performed. It was approved with protocol number 1397/06.

RESULTS

Of the 26,588 births from January 2000 to December 2005, malformations were observed in 975 newborns (3.67%–95%CI 3.44–3.9) and 95 presented with CNS malformations (3.67% (IC=95%, 3.44–3.9)). The annual distribution of these malformations is illustrated in Figure 1 and the prevalence of specific malformations may be evaluated in Figure 2.

Clinical characteristics of both cases and controls are presented in Table. Maternal age ranged from 15 to 44 years. Forty-six per cent of mothers were 15–20 years-old, and only 1.7% were over 40 years-old. Most families lived in the state capital (60.6%) and its metropolitan area (33.7%), while 5.7% came from other cities. Method of delivery was vaginal in 56.8% of the births, cesarean in 42%

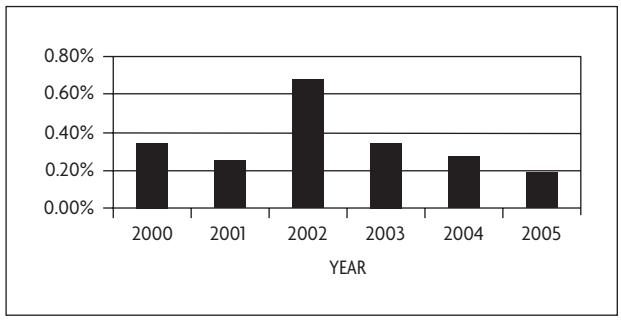

Fig 1. Annual prevalence of neurological malformations.

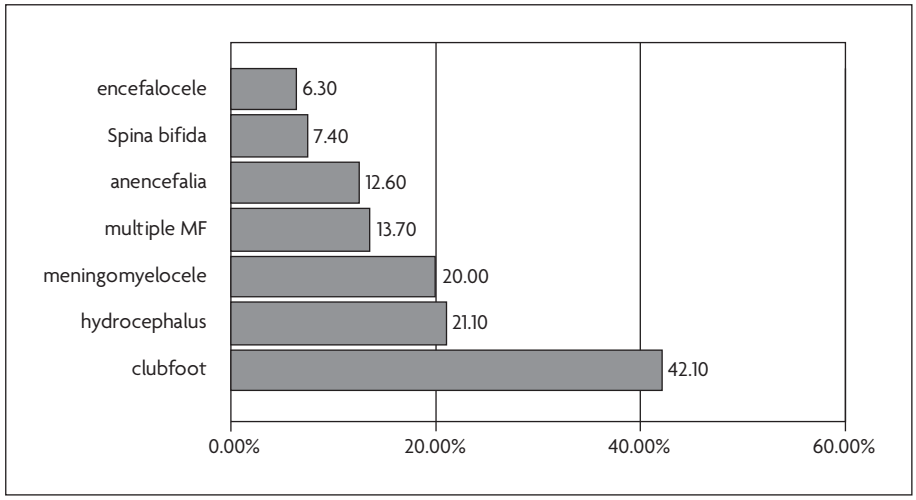

Fig 2. Prevalence of specific neurological malformations.

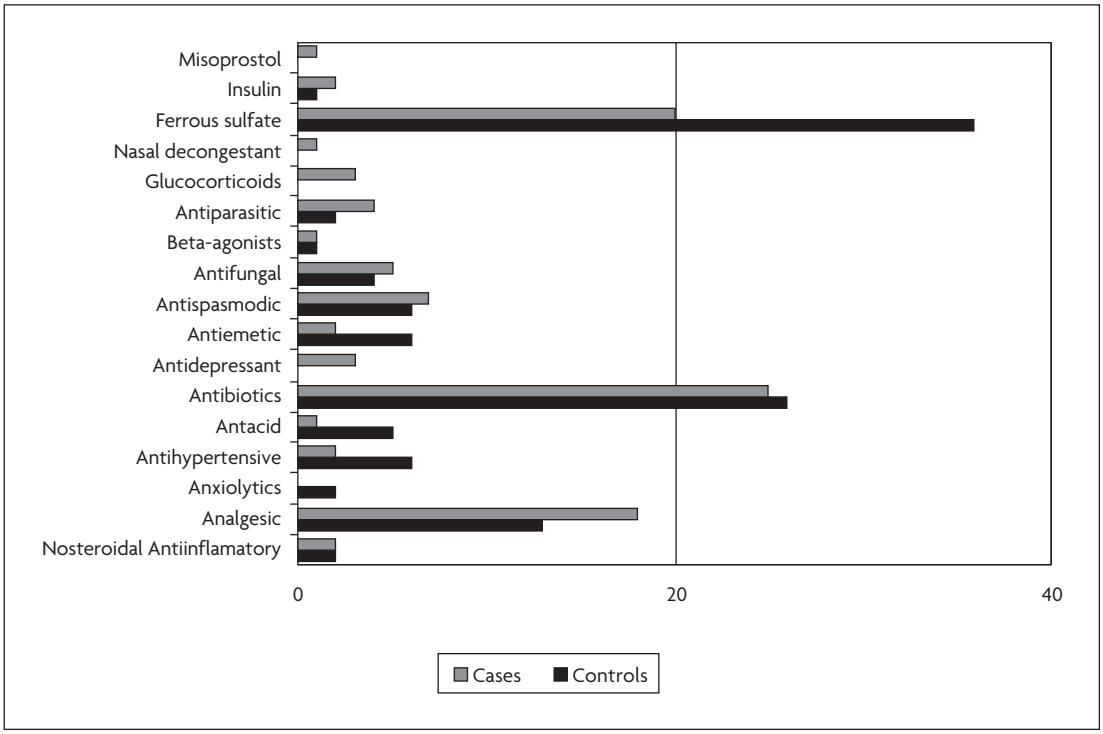

Fig 3. Medications frequently used during pregnancy.

and with the use of forceps in 1.1%. Most mothers were white (75.2%) and had only basic education (46.1%). Reported frequency of malformations in families was 11.7%, and of consanguinity 1.7%.

Most mothers used at least one medication during pregnancy (74.1%). Medications most frequently used are illustrated in Figure 3.

Malformation diagnosis was stablished during the first day of life in 78.7% of the cases, and prenatally in 21.3%. The most frequent neurological malformations were: congenital clubfoot, hydrocephalus and meningomyelocele (n=95, Fig 2). Other malformations included microcephaly (3.2%), craniosynostosis with neurologic alterations (2.1%), holoprosencephaly (2.1%), macrocephaly (2.1%), Arnold Chiari syndrome (2.1%), ocular hypertelorism (1.1%), Moebius syndrome (1.1%), agenesis of the corpus callosum (1.1%) and squizencephaly (1.1%).

Comparing cases and controls, it is possible to observe that CNS malformations cases presented with younger maternal age, smaller birth weight, greater cephalic perimeter, a greater proportion of premature births and smaller Apgar índices in the 1st and 5th minutes (Table).

Table. Clinical characteristics of cases and controls.

Variable	Case	Control	p
Maternal age (years)	24.82±7.042	27.81ffl 6.753	.005
Number of pregnancies	2.56±1.897	3.00±2.011	.131
Lenghth (cm)	49.37±3.08	49.96±1.72	.241
Toracic perimeter (cm)	32.88±2.52	33.32±1.76	.330
Weight (kg)	2801.64	3095.68	.015
Cefalic perimeter (cm)	36.86±5.69	34.53±1.35	.003
Gestational age	35.23±4.058	38.54±2. 074	.000
Number of prenatal follow up visits	7.27±4.506	7.06±3.237	.724
Number of ultrasonographic examinations during pregnancy	3.05±2.335	1.96±1.518	.001
Apgar 1	6.0247±3.35773	8.1667±1.06193	.000
Apgar 5	7.2346±3.38479	9.3038±.62746	.000

Fetal distress was more commonly observed in cases than in controls (28.73%, p=0.006).

There was no differences between cases and controls regarding premature birth, urinary infection or fetal growth restriction, alcohol use, drug use, maternal and paternal schooling.

We observed a greater frequency of the other malformations in the family of cases (16.1%) than controls (6.9%) (p=0.065). Consanguinity was very uncommon in the present sample and was not associated with neurological malformations.

Meningomyelocele was associated to female sex (73.7%, p=0.015), β-agonists (16.7%, p=0.016) and corticoesteroids use (11.1%, p=0.029).

Insulin use (10.5%, p=0.029) was more frequent in cases with hidrocephalus than in controls .

DISCUSSION

The global incidence of malformations was 3.67%, according to other reports in the literature that describe an incidence of 2-5% of significant structural anomalies[13]. In this study about malformations in southern Brazil, we observed that neurological malformations, including clubfoot, comprised almost ten percent of cases. In some studies, CNS malformations are described as the most common type of malformation, comprising up to 13% of cases[14], second only to congenital heart disease[4]. These malformations contribute significantly to mortality and morbidity due to congenital disease during the first year of life[3].

NTDs represent the most important group of CNS malformations, and occur due to failure of spontaneous closure of the neural tube beween the third and fourth week of gestational age[1]. Although the exact cause of NTDs is still unknown, there is evidence suggesting that many factors may adversally influence fetal development, including radiation, drug use, chemical substances and genetic factors[15].

The most frequent malformations in our study were clubfoot, hidrocephalus e meningomyelocele. In other studies, this order may vary slightly[1]. In the United States, anencephaly and spina bífida are the most commonly described CNS malformations, affecting 1:1000 gestations, and more than 300,000 patients worldwide[10].

Both spina bífida and anencephaly are significant causes of infant and fetal deaths[16]. Children with anencephaly usually die at birth or with a few hours of life. Children with spina bífida that do survive are at increased risk for permanent incapacities and psychosocial dificulties[17]. Clinical problems such as paralysis, hydrocephalus Arnold-Chiari tipo II, siringobulbia, siringomielia and endocrine dysfunction may result from the defect itself or from its repair[17].

In this study, we included congenital clubfoot as a neurological malformation because it is known that neurological factors producing medullar or nerve alterations are paramount in its etiology. The normal joint development intrauterus depends on proper functioning of the fetal CNS, on its capacity to move inside the womb and on the amniotic fluid quantity.

Along the last 25 years, many studies have shown that genetic and environmental factors play an important role in the etiology of NTDs[5]. In the present work, we observed that maternal age was negatively associated with the presence of these malformations. Other authors show an U-shaped relationship, with higher incidences in ages below 20 years or above 35 years[18].

Prenatal care is improving in Brazil and in many countries worldwide. We observed that cases performed a higher number of ultrasonographic examinations, dem-

onstrating the importance of careful screening and follow-up for these patients[8].

Our study failed to show a relationship between maternal smoking and CNS malformations, although this relationship is described in the literature. Some authors found a moderate increase in CNS malformations with daily maternal exposition to passive smoking[19].

There is a consistent body of evidence showing that the incidence of CNS malformations could be cut to half if folic acid supplementation would be implemented from the periconceptional period to the initial months of gestation[20-22]. Aiming to reduce the incidence of CNS malformations, many countries are recommending to add folic acid to commonly consumed foods. In the United States, this lead to a 19% reduction of CNS malformations[1].

In summary, it s very important to examine specific causes of CNS malformations in our setting, since there is still many gaps in the understanding of their complex etiology. This kind of study may provide insights to a better planning of preventive policies that have shown to be effective in other contexts.

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