Abstract

Objectives: To evaluate the prevalence and factors associated to neural tube defects in liveborn and stillborn infants delivered at the Hospital das Clínicas, UFMG, from January 8, 1999 to July 31, 2000.

Methods: This is a descriptive study, based on a database, according to the Latin-American Collaborative Study of Congenital Malformation (ECLAMC) rules. Reports on liveborn and stillborn infants with congenital anomalies were prepared including information about morphological description, necropsy results, complementary exams, family, social and pregnancy histories and other clinical data. Each malformed liveborn infant originated a control of the same sex, without malformations. The liveborn and stillborn infants with neural tube defects delivered during that period were classified according to their defect and the presence or absence of associated defects. The liveborn and stillborn infants with neural tube defects were compared to newborns without neural tube defects according to their weight and sex and their mother’s age and parity. Epi-Info 6.0 Program was used for the statistical analysis of the results.

Results: The prevalence of neural tube defects was 4.73 to 1,000 deliveries (89:18,807); it was significantly higher among stillborn infants (23.7:1,000) than among liveborn infants (4.16:1,000), p < 0.001. Neural tube defects were more often found among low weight liveborn infants (<2,500 g), p < 0.001 and less frequently among women who had had more than three gestations, p = 0.007. No association was found regarding newborn’s sex or maternal age. There was no association with newborn’s sex and weight, maternal parity or age among stillborn infants. The liveborn and stillborn infants with neural tube defects were compared to newborns without neural tube defects according to their weight and sex and their mother’s age and parity. Epi-Info 6.0 Program was used for the statistical analysis of the results.

Conclusion: The neural tube defect prevalence found in this study was higher than the one described in international and Latin-American literature.


Introduction

Neural tube closure defects (NTCD) are common congenital deformities which occur due to a failure to adequately close the embryonic neural tube during the fourth week of embryogenesis.1,2 They present varying clinical spectra the most common of which are anencephaly and spina bifida.3
Neural tube defects and associated factors... – Aguiar MJB et alii

Anencephaly is the partial or complete absence of the brain and skull. Spina bifida is a defect in the closure of the laminar arch. The defect can be covered by essentially normal skin (spina bifida occulta) or can be associated with a cystic protrusion which may contain abnormal meninges and cerebrospinal fluid - meningocele; or elements of the spinal marrow and/or nerves- myelomeningocele. Another clinical form encountered is encephalocele in which the brain and meninges develop hernia due to a defect in the calvarium. Approximately 20% of children affected by NTCD present one or other associated congenital defect.

Although varying considerably across different geographic regions, the incidence of NTCD is generally around 1:1000 live births. The risk of recurrence during future pregnancies if a couple has a child with NTCD is between 25 and 50 times greater than that of the general population which is between 4 and 5%.

While NTCD has a heterogeneous etiology a large number of different mechanisms have been described as being involved in its genesis, the great majority of cases are attributed to an interaction between various genes and environmental factors, which is denominated as multifactor inheritance.

The manner in which the genetic mechanism acts is not yet completely clear, but there is strong evidence of its involvement. Studies demonstrate that first degree relatives have a greater risk of NTCD than more distant ones. Another line of evidence is the presence of NTCD in a number of different genetic syndromes such as the Meckel-Gruber syndrome, the Waardenburg syndrome and Trisomias of chromosomes 13 and 18.

It has been proposed that a number of genes are involved in the closure of the neural tube. Some of these genes may confer a strong genetic component while others may only produce a small effect or interact with other genes. Three ‘candidate’ genes which have been studied the most are those which are associated with folic acid metabolism, such as 5, 10-methylenetetrahydrofolate reductase. Many researchers have reported a significantly increased frequency of homozygotes of the C677T mutation of this gene in sufferers and their mothers.

In addition to genetics, various environmental factors also appear to be involved in the etiology of NTCD. Folic acid represents the most important risk factor for NTCD identified so far. The exact mechanism by which folic acid is involved in the embryogenesis of the neural tube is yet to be understood. It is known that periconceptional supplementation continued for the first three months of pregnancy has reduced both the risk of occurrence and the risk or reoccurrence of NTCD by around 50 to 70%. The CDC recommends a dose of 0.4 mg /day for women who are planning a pregnancy and who have a family history of NTCD. For high risk women with previous history of children with NTCD, the recommendation is 4 mg/day.

Other teratogenic agents possibly involved as NTCD risk factors are: maternal Diabetes Mellitus, the use of valproic acid for the treatment of epilepsy during pregnancy, maternal obesity, zinc deficiencies, hyperthermia.

NTCD are important determinants of perinatal morbidity and mortality. All anencephalic children are stillborn or die soon after birth. Children with meningocele and myelomeningocele have higher survival rates, generally due to extensive medical care and surgery. The risk of death is dependant of the severity of the lesion and on other factors such as the availability of medical and surgical resources. Spina bifida occulta may even evolve asymptomatically throughout the life of the patient.

A child with meningocele or myelomeningocele may present with serious, chronic incapacities, such as limb paralysis, hydrocephalus, deformities of the limbs and spinal column, vesical, intestinal and sexual dysfunctions and learning difficulties with risks of psycho-social maladjustment. In the United States the lifetime costs involved for each child with spina bifida is estimated at approximately $294.000.00.

Due to the serious nature of NTCD and their high morbidity and mortality genetic counseling, dietary supplementation with folic acid and pre-natal diagnosis of neural tube defects become extremely important. This can be achieved using ultrasound during gestation and Alfa Feto protein doses, to the amniotic fluid, the levels of which are increased, through amniocentesis between the 14th and 16th weeks of gestation.

We have very little data available on the impact of NTCD amongst us which has great importance in the definition of the best strategy for reducing its incidence.

Since 1967, the Latin American Collaborative Congenital Deformity Study (ECLAMC - Latin American Collaborative Congenital Deformity Study) has undertaken epidemiological and clinical research into congenital anomalies and their causes in hospital births with coverage of more than 100 hospitals in nine South American countries, many of them situated in Brazil. In 1994 it was recognized by the World Health Organization as a Center for the Prevention of Congenital Deformities. More than four million births have already been examined during its 35 years of existence. The prevalence neural tube closure defects for these births was around 1.5:1.000 births. The maternity unit of the Hospital das Clínicas at UFMG has been associated to ECLAMC since 1 August 1990.

The objective of this study is to evaluate the prevalence of and factors associate with the varying types of neural tube closure defects in 18,807 consecutive births, over ten years (August 1990 to July de 2000) observation of congenital defects at the Maternity Unit of the Hospital das Clínicas of UFMG (HC-UFMG).
Material and methods

Since the association of the Maternity Unit of the Hospital das Clínicas da UFMG to the Latin American Collaborative Congenital Deformity Study (ECLAMC) a database has been maintained of all live births (LB) and stillborn infants (SB) with congenital deformities and their controls. A form, standardized by the ECLAMC, is completed on each LB or SB with deformities, on which are noted the morphological description, necropsy data, the results of supporting tests, intercurrent conditions during pregnancy, family history of congenital deformity, consanguinity, sex and weight of the NB, twinning, previous births and maternal age, type of delivery, presentation and socio-economic aspects. For each deformed LB a control LB was chosen defined as the first LB, after the case, of the same sex with no deformities. For each control LB the same data is collected Controls are not used for SBs. Birth reports are generated monthly on the number of LBs and SBs classified by sex, weight (grouped by 500 g intervals) maternal age (grouped by 5 year intervals) maternal parity and multiple births.

A descriptive studied was performed based on this database. Anomaly records and monthly birth reports were reviewed and all SBs and LBs with NTCD identified. We compared the sex, weight, age and number of previous births of these patients with other LBs and SBs born in the hospital during the same period. NTCD cases found were identified according to their clinical presentation (anencephaly, encephalocele, meningocele, myelomeningocele) being classified as isolated deformities, as components of syndromes and/or sequences, associated with other anomalies of the central nervous system or in other organs or systems or as presenting polymalformation (associated with multiple deformities but with no diagnosis of a syndrome). The statistical analysis of data was performed with the Epi-Info 6.0 program with the Chi-squared and Fisher exact tests being used where indicated.

Results

Within the period studied there were 18,807 births, of which 18,258 were LBs and 549 SBs. Eighty-nine cases of NTCD were diagnosed (a prevalence of 4.73:1,000). Seventy-six cases were LBs (a prevalence of 4.16:1,000) and 13 cases were SB (prevalence of 23.7:1,000). The prevalence NTCD among SBs was significantly higher (p < 0.001).

The frequency of NTCD was greater among low birth weight LBs (< 2,500 g) p < 0.001 (Table 1) and less frequent among the children of mothers who had had multiple births (more than three pregnancies) p = 0.007 (Table 1). There was no association with maternal age or sex.

There was no association of any of the factors investigated with SB: sex, weight, number of previous births and maternal age.

Out of the 89 NTCD cases, 42 (47.2%) were myelomeningocele, 24 (26.9%) anencephaly, 15 (16.9%) encephalocele, five (5.6%) meningocele and three were (3.4%) cases of association between two types of NTCD (two cases of anencephaly + myelomeningocele and one of encephalocele + meningocele) (Table 2).

Of the 76 LBs with NTCD, 54 (71.1%) presented with the defect as a single anomaly (myelomeningocele 30 cases, anencephaly 11 cases, encephalocele nine cases and

<table>
<thead>
<tr>
<th>Table 1 - Associated factors of neural tube closure defects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristics</strong></td>
</tr>
<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>Birthweight</td>
</tr>
<tr>
<td>≤ 2,500 g</td>
</tr>
<tr>
<td>&gt; 2,500 g</td>
</tr>
<tr>
<td>Non specified: 90 LB</td>
</tr>
<tr>
<td>Number of pregnancies</td>
</tr>
<tr>
<td>≤ 3</td>
</tr>
<tr>
<td>&gt; 3</td>
</tr>
<tr>
<td>Non specified: 23 LB</td>
</tr>
</tbody>
</table>

Non significant: sex and maternal age.

Table 2 - Type of neural tube closure defects in live newborns

<table>
<thead>
<tr>
<th>Type of NTCD</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelomeningocele</td>
<td>42</td>
<td>47.2%</td>
</tr>
<tr>
<td>Anencephaly</td>
<td>24</td>
<td>26.9%</td>
</tr>
<tr>
<td>Encephalocele</td>
<td>15</td>
<td>16.9%</td>
</tr>
<tr>
<td>Meningocele</td>
<td>5</td>
<td>5.6%</td>
</tr>
<tr>
<td>Two defects</td>
<td>3</td>
<td>3.4%</td>
</tr>
<tr>
<td>Total</td>
<td>89</td>
<td>100%</td>
</tr>
</tbody>
</table>

NTCD: neural tube closure defects.

Among the thirteen SBs, five (38.5%) presented NTCD as an isolated deformity, all of them with anencephaly. In another five cases (38.5%) there was anencephaly associated with deformities in other systems, primarily the cardiovascular and digestive. In two cases (15.4%) anencephaly and myelomeningocele were found with no other deformities. In one case (7.7%), the NTCD found was part of the Meckel-Gruber syndrome (Table 3).

Table 3 - Presentation of neural tube closure defects in liveborn infants

<table>
<thead>
<tr>
<th>Presentation</th>
<th>LB</th>
<th>SB</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTCD with single defect</td>
<td>54 (71.1%)</td>
<td>5 (38.5%)</td>
</tr>
<tr>
<td>NTCD with sign (in one syndrome)</td>
<td>7 (9.2%)</td>
<td>1 (7.7%)</td>
</tr>
<tr>
<td>NTCD associated with malformation of other organs and systems</td>
<td>7 (9.2%)</td>
<td>5 (38.5%)</td>
</tr>
<tr>
<td>NTCD in a pattern of multiple anomalies without defined syndrome diagnosed</td>
<td>5 (6.6%)</td>
<td>0</td>
</tr>
<tr>
<td>NTCD associated with other malformations of the central nervous system</td>
<td>3 (3.9%)</td>
<td>2 (15.4%)</td>
</tr>
</tbody>
</table>

Discussion

The prevalence of NTCD found in our hospital was elevated in comparison with that described in the literature\(^5,6\) and with that recorded by the ECLAMC for South America.\(^7\) Two factors could have contributed to the elevated prevalence: The Maternity Unit of the Maternidade do Hospital das Clínicas at UFMG is a local and regional Centre of Excellence in Fetal Medicine which high risk pregnancies are referred along with those for which there is suspicion, or even a diagnosis of a fetal anomaly, also the fact that the Hospital das Clínicas has a surgical correction facility for meningocele, myelomeningocele, and encephalocele.

With the objective of reducing the incidence of NTCD, many countries are approving the addition of folic acid to foodstuffs consumed in large quantities by their populations. In the United States this has led to a decline by approximately 19% in the incidence of NTCD.\(^8,9\) Chile was the first country in South America to add folic acid to food.\(^7\) Taking into consideration the cost of treating meningocele, myelomeningocele and encephalocele we believe that it is time to assess the cost-benefit relationship of the introduction of folic acid into high consumption foodstuffs in our country. The results observed in Chile\(^7\) will be especially valuable to achieving this objective.

The findings of this work also validate the use of ultrasound and of biochemical tests for the pre-natal triage and diagnosis of NTCD.

We found a higher prevalence of NTCD in LBs with low birth weights, which is described in literature\(^4\). This increased prevalence may be the effect of the anomalies themselves of fetal growth or could be due to the greater risk of deformities within this group of newborns.

The lower prevalence of NTCD among the LB children of mothers who had had a number of children found in our study agrees with that described in certain other works.\(^4,18\)

There are reports that NTCD is more common among the female sex and that there is a greater susceptibility to this deformity among mothers aged between 20 and 24,\(^4\) however within our sample such associations were not found.

The greater prevalence of NTCD observed among the SBs reflects the elevated prevalence of deformities among stillborn infants in comparison with infants born alive.\(^18\)

As is described in literature anencephaly was the predominant NTCD among the stillborn.\(^3\) Only one stillborn infant, with Meckel syndrome, presented a NTCD other than anencephaly.

NTCDs primarily present as isolated deformities, with myelomeningocele and anencephaly being the most common among LBs. Among the SBs, anencephaly was the most frequent defect.

References


Corresponding author:
Marcos José Burle de Aguiar
Rua Timbiras, 659/1001
CEP 30140-060 – Belo Horizonte, MG, Brazil
Tel.: +55 (31) 3274.3453
E-mail: aguiarmr@terra.com.br