v. 2, n. 61, 2022

International Journal of Health Science

RISK FACTORS THAT INFLUENCE THE DEVELOPMENT OF HYDROCEPHALUS

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Abstract: Introduction: Hydrocephalus is a heterogenous medical entity characterized by dilatation of the cerebral ventricles. It is present in all age groups, however, in neonates it is one of the most common congenital anomalies of the central nervous system resulting in different clinical manifestations and frequently associated with complications that have deleterious consequences in their quality of life. Moreover, its incidence and prevalence present regional and international variations while, simultaneously, it is more common in underdeveloped countries. **Methodology:** This study concerns an analytical, transversal epidemiological cohort aiming to associate the outcome "hydrocephalus" with possible maternal and gestational factors. Analysis was conducted based on a database composed of a set of live birth declarations from 01/01/2015 to 12/31/2019, of mothers living in Mato Grosso state. Bivariate analysis was applied, and prevalence ratio was calculated using the chi-squared test of Mantel Haenszel whilst, for a multiple analysis, Poisson regression was used. **Results:** A sample of 43.218 children were selected from SINASC* database of 16 cities of Mato Grosso state. It was observed that preterm new-borns are 6.31 times more likely to develop hydrocephalus compared to full term babies and there is 2.38 times higher prevalence of hydrocephalus among those children of single, divorced or widowed mothers compared to those of married or in-a-stable-relationship mothers. **Discussion:** These findings are consistent with available literature which confirm that prematurity is one of the most important risk factors for hydrocephalus and that a mother's marital status also plays a role not yet well-understood. **Conclusion:** This research contributes significantly to the study of gestational and maternal causes related to neonates born alive with hydrocephalus, since

it exposes plenty of knowledge concerning these factors which are relatively scarcely approached in other sources regarding this topic.

*SINASC stands for National Information System on Live Births which is a Brazilian database open to the public.

Keywords: congenital hydrocephalus, risk factors, premature infant.

INTRODUCTION

Hydrocephalus is currently understood as a medical entity of heterogeneous etiology, characterized by an abnormal dilation of the cerebral ventricles, called ventriculomegaly, that can occur, basically, by three mechanisms: increase in the production of cerebrospinal fluid (CSF), obstruction in some level of the ventricular circulatory system or by a failure in the blood reabsorption of the cerebrospinal fluid[1, 2, 3].

Any of these mechanisms can develop at any age and is one of the most common congenital anomalies of the central nervous system (CNS) in neonates, with incidence and prevalence showing regional variations. In this context, the incidence in newborns ranges from 0.3 to 2.5 cases per thousand live births[4, 5].

The mechanisms that lead to brain injury are still not fully understood. Thus, changes in brain structure can lead to hydrocephalus, as far as the development of this pathology can also lead to structural damage around the ventricles. In this sense, the increased intraventricular pressure can distend and compress the periventricular tissue, resulting in ischemia, hypoxia and cerebral edema[1, 6].

The pathology in question can be classified in several ways, the most used being the classification of Walter Dandy (1913), who divided it into communicant, in which there is no obstruction, and non-communicant, where there are signs of obstruction limiting communication of cerebrospinal fluid between the ventricles. Furthermore, McCullough (1989) created an etiological classification widely used in current studies, dividing it into acquired or congenital, obstructive or non-obstructive and syndromic or non-syndromic[7].

The most recent classification dates from 2011, called "the Multi-Categorical Hydrocephalus Classification", which is composed of ten categories and fifty-four subtypes. There are two more forms of hydrocephalus that deserve to be mentioned, ex-vacuum, resulting from atrophy of neuronal tissue in the periventricular region, leading to an apparent ventriculomegaly, and normal pressure, very common in the elderly and in sequelae of perinatal anoxia. In short, when considering the variety of classifications, the complexity of this disease becomes evident[7].

In previous studies, it was shown that the development of congenital hydrocephalus is closely related to exposure to risk factors, which can be divided into maternal, gestational and perinatal. Among the maternal factors, the following stand out: chronic arterial hypertension, preeclampsia, eclampsia, history of previous miscarriage, recurrent miscarriage, chronic diabetes mellitus, use of medications (misoprostol, metronidazole, antidepressants and especially isotretinoin), smoking, malnutrition, obesity, single marital status and level of education[8,9].

Regarding gestational factors, the following are evident: inadequate prenatal care, gestational diabetes mellitus, placental abruption, prematurity, intrauterine infections (TORCHS, enterovirus, lymphocytic choriomeningitis) and intrauterine hypoxia. Finally, there are perinatal factors that are divided into: perinatal hypoxia and prolonged labor[8,9].

The clinical manifestations of congenital hydrocephalus vary according to age group,

etiology, level of obstruction to cerebrospinal fluid flow, level of intracranial pressure, malformations and other associated conditions. In newborns, the most common findings are irritability, vomiting, and increased head circumference on physical examination. The main indications in infants are: craniofacial disproportion, bulging fontanelles regardless of the patient's position, setting sun sign and convergent strabismus, cranial sutures enlargement, increased head circumference, cervical hypertonia and decreased mobility of the lower limbs[10, 11].

Diagnosis is made through a suggestive clinical examination complemented by neuroimaging. CT or magnetic resonance imaging are the gold standard tests, which more accurately provide a skull overview. Furthermore, transfontanellar ultrasound can also be used, but it has limitations visualizing lateral structures[11, 12].

Treatment can be pharmacological or surgical. Drugs used in conservative procedures are intended to inhibit CSF production. However, this conduct is not so effective due to its transience and side effects. Thus, surgical options are the most used, such as ventricular shunts through valves to the peritoneum[1].

Although this pathology can be surgically corrected, there are still deaths and a wide variety of sequelae due to multiplicity of causes and associated comorbidities, which can be: motor, cognitive, psychiatric, neuroendocrine and social aspects. Among these, the most feared are those that result in immobility (such as periventricular leukomalacia), hearing and visual loss, epilepsy, mental retardation, and severe delay in neuropsychomotor development. Other sequelae include depression, cognitive impairment, school delay, and chronic headache[13, 14, 15, 16].

The relevance of this study can be appreciated since it is a disease of high complexity and morbidity. As a result, there is a significant loss of quality of life for patient and their family. However, when diagnosis and treatment are made earlier, it is possible to limit complications and impact on outcomes. Therefore, identifying risk factors that predispose to hydrocephalus, it would be possible to be alert during prenatal care to those most vulnerable mothers and, thus, be able to establish a diagnosis and conduct in the earliest stages of the disease[17, 18, 19].

Therefore, the present research aims to analyze the influence of gestational and maternal causes on live births with hydrocephalus in Mato Grosso State, to discuss and elucidate the relationship of those factors with the development of the pathology.

METHODOLOGY

This is an observational analytical cross-sectional study that seeks to associate the hydrocephalus outcome with the possible gestational and maternal factors to which live births were exposed in order to assess whether there is a relationship between the variables, which would justify the development of the pathology. The analysis was made from a database composed of the set of declarations of live births that occurred in the period from 01/01/2015 to 12/31/2019, from mothers residing in the State of Mato Grosso. The Information System on Live Births (SINASC) was used as a data source, which has universal coverage. The declaration of live births (DN) is filled in both by live births assisted by the SUS (Unified Health System) and by those assisted by health insurance plans or by direct payment.

The variables contained in the DN were included in the analysis, classified as independent variables: agribusiness region (yes, no), region of low human development index - HDI (yes, no), age group at risk (at

risk, not at risk) , marital status (married/ consensual union, single/separated/widowed), years of schooling (up to 3 years, 4 or more), occupation, work with pesticides (yes, no), dead children (yes, no), prematurity (yes, no), number of prenatal consultations (up to 6, 7 or more), primiparous (yes, no), previous cesarean section (yes, no) and sex of the live birth (male, female).

According to a literature review, it was concluded that the maternal age group considered at risk for the development of fetuses with hydrocephalus includes mothers under 18 and over 36 years of age. The response variable was live births with hydrocephalus and data were analyzed using variable frequencies, measures of means and standard deviations.

The variables were described in absolute (n) and relative (%) frequencies. In the bivariate analysis, associations were identified between the response variable (hydrocephalus) and the other exposure variables. To calculate the statistical significance of the association, the Chi-Square test was used using the Mantel-Haenszel method (95% CI). Variables with $p \leq 0.25$ were selected for multiple analysis using Poisson Regression. After progressive removal of variables (stepwise backward), those whose significance level remained ≤ 0.05 were kept in the final model.

The accomplishment of this work does not require the application of the Free and Informed Consent Form (Res. CNS 466/2 in its chapter IV.8), since it is a descriptive study with information contained in notification forms, without disclosing the names of the victims, which will be kept confidential, in accordance with the provisions of Resolution 466/12 of the National Health Council.

RESULTS

In total, 43,218 children were selected from the SINASC database from sixteen municipalities Mato Grosso State. More than half of the participants were male (51.04%). As for the gestational age, about 90% (89.31%) of the children were born at term. Regarding twins, only 1.67% were twins (Table 1).

Regarding maternal variables, there was a predominance of the non-risk age group (85.95%). About 80% (79.18%) of the mothers do not declare themselves as white. In terms of education, 97.21% had 4 years or more of study. About 2/3 (66.17%) of the mothers declared themselves to be married/in a consensual union (Table 1).

Regarding housing, 67.51% did not live in a low HDI region. Regarding the region of residence, 74.67% did not live in an agribusiness region and regarding their current occupation, 99.17% did not work with pesticides (Table 1).

As for the gestational variables, 63.69% had other pregnancies, of which almost 70% (67.73%) had not had cesarean sections before. Just under 20% (18.19%) have had dead children. Regarding the number of prenatal consultations, 67.60% had 7 or more consultations (Table 1).

Table 2 presents the crude prevalence ratio for hydrocephalus associated with the maternal and gestational characteristics of the patients. Premature newborns had 6.31 (95%CI 3.96 – 10.06) times greater occurrence of hydrocephalus when compared to full-term newborns. There was a higher prevalence of hydrocephalus among participants born to single/separated/widowed mothers, 2.38 times higher when compared to those born to married/consensual unions (Table 2).

In the multiple analysis using Poisson regression, the variables marital status (absence of a stable union) and prematurity remained in the model, which maintained a statistically significant association with hydrocephalus (Table 3).

Variables	n	%
Age group (43.218)		
1- At risk	6070	14,05
2- Not at risk	37148	85,95
Sex (43.218)		
Male	22060	51,04
Female	21158	48,96
Mother's race/color [a] (42.676)		
1- Other	33790	79,18
2- White	8886	20,82
Years of education [b] (43.083)		
1- up to 3 years	1204	2,79
2- 4 or more years	41879	97,21
Marital status [c] (42.893)		
1-Single/divorced/widowed	14510	33,83
2-Married/consensual union	28383	66,17
Primiparous (43.218)		
1- Yes	15693	36,31
2- No	27525	63,69
Dead children [d] (41.843)		
1.Yes	7610	18,19
2. No	34233	81,81
Premature (43.218)		
1- Yes	4622	10,69
2- No	38596	89,31
Twins [e] (43.217)		
1-Yes	720	1,67
2-No	42497	98,33
Previous cesarean section [f] (41.987)		
1- Yes	13550	32,27
2-No	28437	67,73
Nº prenatal consultations [g] (42.998)		
1- Up to 6	13932	32,40
2- 7 or more	29066	67,60
Works with pesticides (43.218)		
1- Yes	360	0,83
2- No	42858	99,17
Agrobusiness region (43.218)		
1- Yes	10948	25,33
2- No	32270	74,67
Low HDI region (43.218)		
1-Yes	14041	32,49
2-No	29177	67,51

a), b), c), d), e), f), g) Information for some of these variables was lacking.

Table 1. Maternal and gestational profile of hydrocephalus cases (43218) in sixteen municipalities in Mato Grosso between 2015 and 2019.

Variables	%	RR	IC95%	p*
Age group				
At risk	0,21	1,35	(0,74 – 2,46)	0,327
Not at risk	0,16	1,00		
Sex				
Male	0,19	1,42	(0,89 – 2,28)	0,140
Female	0,14	1		
Mother's color/ethnicity				
Other	0,18	1,43	(0,75 – 2,73)	0,268
White	0,12	1		
Years of education				
Up to 3 years	0,33	2,08	(0,76 – 5,68)	0,146
4 or more years	0,16	1		
Marital status				
Single/separated/widowed	0,27	2,38	(1,49 – 3,80)	<0,001
Married/consensual union	0,11	1		
Primiparous				
Yes	0,18	1,18	(0,74 – 1,89)	0,484
No	0,16	1		
Dead children				
Yes	0,20	1,23	(0,69 – 2,17)	0,482
No	0,16	1		
Prematurity				
Yes	0,67	6,31	(3,96 – 10,06)	<0,001
No	0,11	1		
Twins				
Yes	0,14	0,83	(0,11 – 5,97)	0,854
No	0,17	1		
Previous cesarean section				
Yes	0,13	0,69	(0,40 – 1,18)	0,175
No	0,18	1		
Nº prenatal consultations				
Up to 6	0,20	1,33	(0,83 – 2,13)	0,239
7 or more	0,15	1		
Works with pesticides				
Yes	0,28	1,68	(0,23 – 12,03)	0,603
No	0,17	1		
Agrobusiness region				
Yes	0,21	1,38	(0,84 – 2,27)	0,197
No	0,15	1		
Low HDI region				
Yes	0,14	0,74	(0,44 – 1,26)	0,269
No	0,18	1		

Table 2. Prevalence and prevalence ratio according to maternal and gestational characteristics of hydrocephalus cases (n=43218) in sixteen municipalities in Mato Grosso between 2015-2019.

Variables	PR Crude	IC	p value	Adjusted PR	IC	p value
Years of education						
Up to 3 years	2,08	0,76-5,68	0,146	-	-	-
4 or more years	1,00					
Sex						
Male	1,42	0,89-2,28	0,14	-	-	-
Female	1,00					
Agrobusiness region						
Yes	1,38	0,84-2,27	0,197	-	-	-
No	1,00					
Previous cesarean section						
Sim	0,69	0,40-1,18	0,175	-	-	-
No	1,00					
Marital status						
Single/separated/widow	2,38	1,49-3,80	< 0,001	2,14	1,32 – 3,48	0,002
Married/Consensual union	1,00			1,00		
Nº prenatal consultations						
Up to 6	1,33	0,83-2,13	0,239	-	-	-
7 or more	1,00					
Prematurity						
Yes	6,31	3,96-10,06	< 0,001	6,07	3,73 – 9,90	< 0,001
No	1,00			1,00		

Table 3. Final Poisson Regression Model - Prevalence ratios and 95%IC of predictive variables of hydrocephalus in live births in Mato Grosso, 2015-2019.

DISCUSSION

The present study addressed, through the SINASC database, possible maternal, socio-demographic and gestational causes as a predisposing factor for hydrocephalus. It brought a different perspective not yet seen in other literature, and which has significant importance since it assesses modifiable factors, especially pertaining to public health, such as the number of prenatal consultations and diseases that predispose to prematurity, such as urinary tract infections, gestational diabetes and others.

The studies of Tully HM. and Perdaens O. point out the relationship between hydrocephalus and premature births, especially when correlated with intraventricular hemorrhage. According to Vinchon M, among the newborns observed in the study, there was a predominance of borderline preterm infants (mean gestational age at birth of 36.6 weeks), with a mean borderline weight at birth (2,606g). Although males presented relatively few cases and, therefore, were imprecise, it is worth mentioning that this finding is consistent with reports from several previous studies[8, 9, 14, 15].

Regarding maternal marital status, there is a lack of data in the literature to understand its relationship as a cause of hydrocephalus. Tully HM. points out that mothers of infants with hydrocephalus are more likely to be single (32% of cases vs 28% of controls). The present study reinforces that "single/divorced/widowed" mothers are a risk factor for hydrocephalus, although it was not possible to make associations or justifications for this fact. Delvaux T and Rosa CQ Silveira show this risk factor due to the lower attendance or late start of these mothers to prenatal care, reaching a risk three times greater for not performing appropriate prenatal care when compared to married mothers[20, 21].

Reaffirming what has been exposed in the present study, Melo WA identified in his study a higher proportion of congenital anomalies among late mothers (≥35 years), with this worse perinatal outcome being correlated with the inadequate number of prenatal consultations both among adolescent mothers and among older mothers. However, in his study the higher proportion of single mothers among older mothers is highlighted, when compared to other age groups. Thus, older single mothers represent the highest risk group for newborns with congenital anomalies. It is noteworthy, however, that in their analysis different types of anomalies were found, with the musculoskeletal being the most frequent (41%), while 16% affect the central nervous system, including hydrocephalus.

Prematurity is an important risk factor in several pathologies and can be avoided, in some situations, with proper medical monitoring during pregnancy. Preterm delivery can predispose to diseases such as intraventricular hemorrhage, an important cause of hydrocephalus due to fragility in the germinal matrix.

The main limitation of the present study was the SINASC database, which presented two obstacles. The first was the non-completion of the system form by the responsible professionals, causing a gap in the bank. And the second, the moment of filling out the form, since most hydrocephalus develop during the first year of life and SINASC register only children with hydrocephalus at birth, not clarifying the diagnostic criteria used for the diagnosis of these children.

To complete the vision of this work, a study could be carried out expanding the moment of diagnosis of the disease, using other databases, to reach a greater number of children with hydrocephalus and correlating it with maternal and gestational factors. Another perspective to be analyzed in a future work

would be the correlation between maternal marital status and the risk of developing this pathology, since some studies addressed some consequences of a pregnancy without the support of a partner, but none showed a direct correlation between the marital status and hydrocephalus.

CONCLUSION

The present study pointed out two variables with statistical significance: prematurity and maternal marital status. Moreover, it is concluded that prematurity is the main risk factor associated with hydrocephalus, and individuals born before 37 weeks of gestation have a risk 6.31 times greater than those born at term. With regard to marital status, single, separated or widowed mothers have a 2.38 times higher rate of children with hydrocephalus compared to mothers who are married or in a consensual union. Therefore, the analysis of the variables allowed the achievement of the objective proposed by the study.

The work contributes in an important way to the study of gestational and maternal causes related to live births with hydrocephalus, since it expands knowledge about these factors, which are still little addressed in the bibliographic sources. Therefore, a better understanding of these variables allows for improvement on the clinical history of patients with greater susceptibility to develop it, by enabling a more accurate search for risk factors by health professionals who are involved in prenatal care, thus contributing, indirectly, to a possible reduction in the incidence of hydrocephalus.

ACKNOWLEDGMENTS

With great joy, we first thank God for the completion of this research. We also express our immense gratitude to our supervisors Dr. Wanclis Pinheiro Poussan, Dr. Ageo Mário C. Silva and Dr. Heloise Helena Siqueira, for their support, trust and commitment dedicated to the preparation of this work. Our thanks also goes to the entire general skills team, professors Dr. Emerson GP Favaro, Dr. Luciana Marques da Silva, Dr. Ageo Mário C. Silva and Dr. Rosa Maria Elias, during these 4 years, for laying out the foundations and passing on solid scientific knowledge in methodology, which was extremely important for our training.

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