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Original

Factors associated with brain and pre-brain arteriovenous malformation: a case control study

Fatores associados com malformações arteriovenosas cerebrais e pré-cerebrais: um estudo de caso-controle

Factores asociados a malformaciones arteriovenosas cerebral y precerebral: estudio de casos y controles

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Resumo

Introdução. As malformações arteriovenosas cerebrais e pré-cerebrais (MAVCs) são uma causa importante de AVC hemorrágico entre jovens, embora sejam normalmente uma condição congênita, podem facilmente passar despercebidas durante anos. **Objetivo**. Encontrar preditores de MAVCs. **Método.** Estudo caso-controle baseado no banco de dados do Sistema de Informação em Saúde (TABNET), disponibilizado pelo Departamento de Informática do Sistema Único de Saúde (DATASUS). Foram coletadas informações de crianças nascidas com MAVCs (CID Q280 e Q282) no período de 2010 a 2020 e comparadas com todas as outras crianças nascidas no mesmo período. **Resultados.** Foram encontrados 75 casos de MAVCs, sendo 21 pré-cerebrais e 54 cerebrais. O sexo feminino representou 55% (41) dos pacientes. Uma coorte de 40.588.143 neonatos foi utilizada como controle. Os recém-nascidos pré-termo tiveram uma chance aproximadamente 10 vezes maior de ter MAVCs (p<0,001; OR:9,990; IC: 6,347-15,725). O parto cesáreo foi associado a uma chance 63% maior de MAVCs (p<0,001; OR: 0,372; IC: 0,219-0,632). A etnia também se associou a MAVCs, nomeadamente com as brancas a terem 2,2 vezes mais chances de ter MAVCs (p=0,001; OR: 2,242; CI:1,379-3,643). A gravidez gemelar foi marginalmente associada a MAVCs (p=0,063; OR: 0,361; IC: 0,132-0,989). **Conclusões.** A prematuridade, o parto cesáreo e a etnia branca foram estatisticamente associados a MAVCs. Estes resultados devem ser considerados para orientar estratégias de rastreio e suspeição clínica. Estudos de coorte prospectivos na área são recomendados.

Unitermos. Malformação arteriovenosa; Hemorragia cerebral; Estudo de caso controle

Abstract

Introduction. Brain and pre-brain arteriovenous malformations (BAVMs) are an important cause of hemorrhagic stroke among youth, although are normally a congenital condition, can easily pass unnoticed for years. **Objective**. To find predictors of BAVMs. **Method.** Case control study based in the database of the Health Information System (TABNET), made available by the Informatics Department of the Brazilian National Health System (DATASUS). Information of children born with BAVMs (ICD Q280 and Q282) ranging from 2010 to 2020 was collected and compared with all the other childrens born at the same period of time. **Results.** A total of 75 cases of BAVMs were found, with 21 being pre-cerebral and 54 cerebral. Females represented 55% (41) of the patients. A cohort of 40,588,143 babies was used as control. Preterm newborns had an approximate 10 times higher chance of having BAVMs (p<0.001; OR:9.990; CI: 6.347-15.725). Cesarean birth was associated with 63% higher chance of BAVMs.(p<0.001; OR: 0.372; CI: 0.219-0.632). Ethnicity was also associated with BAVMs, notably with white ones having 2,2 times more chances of having BAVM (p=0.001; OR: 2.242; CI:1.379-3.643). Twin pregnancy was marginally associated with BAVMs (p=0.063; OR: 0.361; CI: 0.132-0.989). **Conclusion.** Prematurity, cesarean birth, and white ethnicity were significantly associated with BAVMs. These findings are worth considering to guide screening strategies and clinical suspicion. Prospective cohort studies in the same topic are recommended.
Keywords. Arteriovenous Malformation; Cerebral hemorrhage; Case-Control Study

Resumen

Introducción. Las malformaciones arteriovenosas cerebrales y preencefálicas (MAVC) pueden propiciar ataque hemorragico, especialmente entre los jóvenes, aunque normalmente son una afección congénita y pueden pasar desapercibidas fácilmente durante años. **Objetivo**. Encontrar predictores de BAVM. **Método.** Estudio de casos y controles basado en la base de datos del Sistema de Información en Salud (TABNET), puesto a disposición por el Departamento de Informática del Sistema Nacional de Salud de Brasil (DATASUS). Fueron colectadas informaciones de niños nacidos con BAVMs (ICD Q280 y Q282) en el período de 2010 a 2020 y comparados con todos los demás niños nacidos en el mismo período de tiempo. **Resultados.** Se encontraron un total de 75 casos de BAVM, siendo 21 pre-cerebrales y 54 cerebrales. Las mujeres representaban el 55% (41) de los pacientes. Se utilizó como control una cohorte de 40.588.143 recién nacidos. Los recién nacidos prematuros tenían aproximadamente 10 veces más probabilidades de presentear BAVM (p<0,001; OR:9,990; IC: 6,347-15,725). El parto por cesárea se asoció con un 63% más de probabilidades de BAVM (p<0,001; OR: 0,372; IC: 0,219-0,632). El origen étnico también se asoció a BAVM, sobre todo en el caso de las blancas, que tenían 2,2 veces más probabilidades de padecer BAVM (p=0,001; OR: 2,242; IC:1,379-3,643). El embarazo gemelar se asoció marginalmente con las MAVD (p=0,063; OR: 0,361; IC: 0,132-0,989). **Conclusiones.** La prematuridad, el parto por cesárea y la etnia blanca se asociaron de forma significante con las BAVM. Merece la pena tener en cuenta estos hallazgos para orientar las estrategias de cribado y la sospecha clínica. Estudios prospectivos de cohortes en el mismo tema
Palabras clave. Malformación arteriovenosa; Hemorragia cerebral; Estudio de casos y controles

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INTRODUCTION

Cerebral and precerebral arteriovenous malformations (BAVM) are congenital vascular anomalies that involve an

abnormal connection between the arteries and veins in the brain or in the adjacent precerebral tissue[1]. These malformations occur during fetal development and result from an abnormal blood vessel network that leads to serious complications[2,3]. They are characterized by a direct communication between artery and vein, without the formation of capillaries, which are responsible for lowering blood pressure before the blood returns to the veins. Thus, the blood flow is directed directly between the two large vessels, causing high pressure[2,3]. These malformations may be associated with an increased risk of stroke[1,2], since stroke corresponds to a brain area in which the blood flow is interrupted, either by a blockage, which corresponds to ischemic stroke, or by bleeding, as in the case of hemorrhagic stroke. In the case of cMAVs, the risk of stroke is related to the bleeding of the malformation rather than to a blockage of blood flow, given the presence of abnormal and fragile vessels associated with high blood pressure[2]. Although the exact cause of this anomaly is not completely understood, there are several genetic and environmental factors that may be associated with cMAVs, such as family history, genetic syndromes, gender, age, history of intracranial hemorrhage (ICH), and related vascular anomalies such as brain aneurysms[3].

The BAVMs are rare, affecting about 0.1% of the population, also representing one-tenth of the incidence of intracranial aneurysms[2,4]. 90% of the lesions occur in the supratentorial space, and the vast majority of them are

single, with multiple lesions only 9%[3,4]. This type of malformation accounts for about 2% of all strokes, 3% of strokes in young adults, and 9% of subarachnoid hemorrhages[4].

The diagnosis is usually challenging due to the scarcity of symptoms until the ICH and it's generally made by means of imaging tests in patients presenting with unexplained seizures, acute neurological deficits or some change in mental status[4]. Computed tomography or magnetic resonance imaging may be used, as well as angiography with computed tomography or magnetic resonance angiography[4]. Thus, in view of the high potential to cause ICH of BAVMs and its challenging diagnosis, we aimed to find potential predictors of this condition.

METHOD

Sample

This is a quantitative, epidemiological, case control approach that analyzed all information of children born with BAVMs (ICD Q280 and Q282) in Brazil ranging from 2010 to 2020. This study uses public data, therefore does not need ethical appreciation according to Brazilian law.

All the records of live births of mothers residing in Brazil. The "control" group consisted of all live births between 01/01/2010 and 12/31/2020, totaling 40,588,143 children. The "case" group was composed of children born with cVAMs, between 01/01/2010 and 12/31/2020, with 75 children.

Procedure

Data from the database of the Health Information System (TABNET) and rom the Live Birth Information System (SINASC), made available by the Informatics Department of the Brazilian National Health System (DATASUS), were used. These were made available by all Secretary of Health of Brazil, in a Tabwin database, which were imported into the Microsoft Office Excel 2023 Program. The linkage technique was used for the union of the databases, using the number of the Certificate of Live Birth as a univocal term. The dependent variable was BAVMs, and the independent variables were organized into three groups: 1. Maternal socioeconomic conditions (age and race); 2. Maternal obstetric (type of pregnancy and type of delivery); 3. Regarding the newborn (gender, weight and gestational age).

Statistical analysis

All variables were compared between cases and controls usine pearson chi-square and odds ratio with a 95% confidence interval and p value being considered significant when <0.05. Data disposed in graphics had their trends calculated by linear regression and had their equations and their R^2 analyzed.

RESULTS

A total of 75 cases of BAVMs were found, with 21 being pre-cerebral and 54 cerebral, and were compared with

40,588,143 newborns without BAVMs (controls). The characteristics of each group and main statistical differences are summarized in Table 1.

Table 1. Demography and statistical differences between cases and controls.

		Cases n	Controls n	p-value	Odds ratio	Confidence interval
Sex	Male	8	20,791,320	0.565	0.762	0.301-1.930
	Female	10	19,796,823			
Ethnicity	White	41	15,595,048	<0.001	-	-
	Black	6	1,747,509			
	Yellow	1	135,939			
	Brown	20	21,136,722			
Maternal age group	15-19 years	2	7,012,724	0.796	-	-
	20-34 years	13	28,151,048			
	35-39 years	2	4,017,524			
	40-44 years	1	990,816			
Gestation time	<37 weeks	10	563,164	<0.001	9.99	6.347-15.725
	37-42 weeks	65	38,254,724			
Type of gestation	Single	71	39,707,542	0.063	0.361	0.132-0.989
	Gemellar	4	808,336			
Type of delivery	Vaginal	18	18,616,744	<0.001	0.372	0.219-0.632
	Cesarean	57	21,923,439			
Number of prenatal appointments	None	1	855,413	0.379	-	-
	From 1 to 3 appointments	2	2,739,482			
	From 4 to 6 appointments	2	10,607,678			
	7 or more appointments	12	26,060,165			

From cases which we have data female represented 55.55% (10), ethnicity was mainly white with 60.29% (41), maternal age group was mainly between 20-34 years 72.22% (13), gestational time concentrated mainly in 37-42 weeks 86.66% (65), type of gestation was predominantly single 94.66% (71), type of delivery was mostly cesarean 76% (57) and number of prenatal appointments ranged mainly from more than seven 70.58% (12).

Preterm newborns had an approximate 10 times higher chance of having BAVMs ($p<0.001$; OR:9.990; CI: 6.347-15.725). Cesarean birth was associated with 63% higher chance of BAVMs ($p<0.001$; OR: 0.372; CI: 0.219-0.632). Ethnicity was also associated with BAVMs, notably with white ones having 2.2 times more chances of having BAVM ($p=0.001$; OR: 2.242; CI:1.379-3.643). Twin pregnancy was marginally associated with BAVMs ($p=0.063$; OR: 0.361; CI: 0.132-0.989).

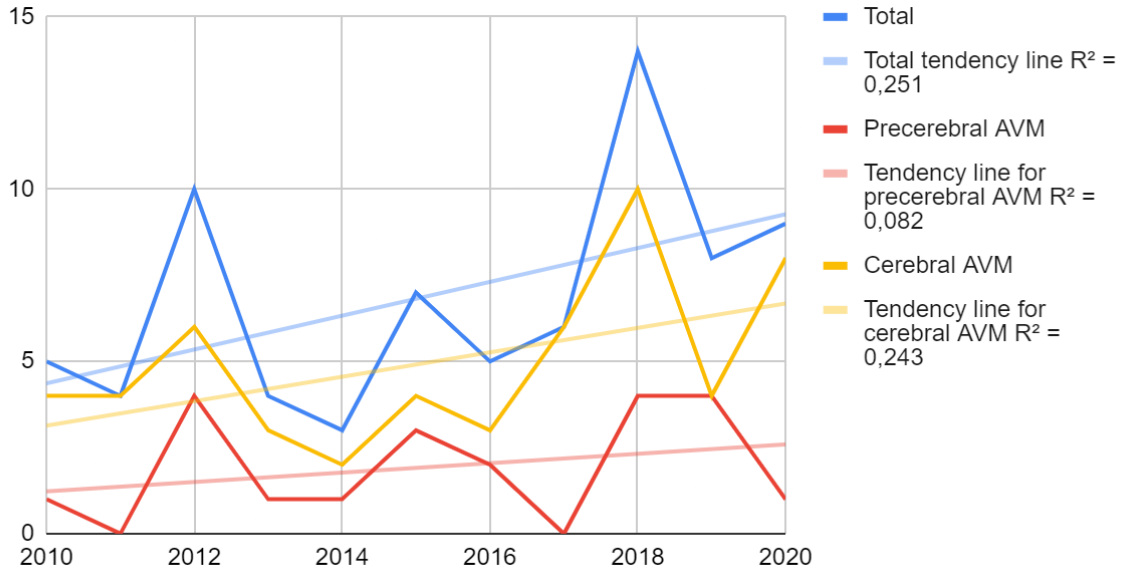
We also find a notable increase in cases of BAVMs through the years of the study ($R^2=0.251$) notably due to the growth in the detection of cerebral arteriovenous malformation ($R^2=0.243$), as seen in Figure 1.

DISCUSSION

Our study evaluated children born with cAMVs and compared them to children born without cAMVs regarding maternal socioeconomic factors, maternal obstetric conditions and newborn characteristics at birth. We analyzed these data to look for possible risk factors that could

influence or be more associated with arteriovenous malformations.

Figure 1. Cases of BAVMs per year.



Our results showed that factors such as ethnicity, gestational age classification and type of delivery were statistically more related to BAMVs, with white ethnicity, prematurity (<37 weeks) and cesarean delivery standing out. The result regarding ethnicity suggests that the disease is related to genetic or socio-environmental factors that affect the white population. Regarding prematurity, our results corroborate the hypothesis that BAMVs are related to the failure of the cerebral vascular system to fully mature or to possible perinatal trauma, especially considering that many BAMVs are related to more superficial vessels (cortical

and subcortical), which develop later[5,6]. Finally, regarding cesarean delivery, a more uncertain relationship to be established would be trauma resulting from this type of procedure or the issue of scheduled birth, which can be performed prematurely. However, there is no relationship of higher risk of neurological outcomes in cesarean deliveries, therefore, lower chances of etiopathogenesis being due to traumas of the procedure[7].

We also found a growing trend in diagnosed cases of BAMVs, probably related to the increase in the number of imaging tests for investigation of central nervous system diseases with incidental results[8].

With regard to the other variables tested, our study did not find an association related to patient gender, which was also found in other studies[9-12]. A certain epidemiological study found variations in the proportions between the sexes affected in different countries, but not relevant to the point of demonstrating significant discrepancies[13].

We know from the literature that there is a prevalence of BAMVs of approximately 50 cases per 100,000 people and that, of these, approximately half present ICH. This shows that, despite their low prevalence, cAMVs pose a great risk to the patient. In addition to hemorrhage, other complications may arise, such as seizures, neurological deficit, headache, among others[14].

Another important point is that one of the main factors related to the appearance of these complications is the lack of follow-up of these patients, in this sense, our study, by

showing possible causal factors for this condition, can be an important point for early screening and consequently for the best prognosis of these patients exposed to significant variables.

In the question of etiologies and risk factors, it is not yet known exactly which mechanisms are involved in the etiopathogenesis of the disease, one of the theories is that the problem occurs due to poor communication between the veins and capillaries during the embryogenesis phase together with the permanence of this problem until birth. In this sense, prematurity would be a possible risk factor, since there was not enough time for the maturation of the vascular architecture[5,6]. Another point is genetic factors: according to the literature, most cAMVS occur as single individual or sporadic lesions that do not have a clear genetic association, but in cases of multiple lesions, it is possible to point out genetic syndromes as causes, such as Hereditary Hemorrhagic Telangiectasia (HHT), an autosomal dominant syndrome associated with blood vessel malformations[14,15].

This syndrome has 5 subtypes discovered, with HHT1 and HHT2 being the most common, representing 87% of cases, the alteration in the ENG gene on chromosome 9q34 is associated with 40-50% of HHT1 cases, and in the case of HHT2, the alteration of ACVRL1 on chromosome 12q13 is associated with 40-50% of cases. Although the percentage of cases is not available, alteration in the GDF2 gene on chromosome 10q11 has also been identified in HHT5 as a possible factor for the disease. Regarding HTT4 and HTT3,

although the related genetic locus is known, the specific gene associated with these two subtypes is not known. Moreover, it is important to highlight a limitation of the genetic study of this syndrome, since in 7-20% of families with HTT, no mutation has been identified[15].

We consider some limitations in this study, highlighting the difficulty in finding literature on BAMVs - mainly similar case-control studies -, environmental risk factors and possible etiologies for the disease. It is also evident that the data are from a country with a multiethnic population, and there is no data such as family history or genetic factors, so the study cannot assess hereditary or mutagenic components. In addition, the study design was affected due to the Brazilian database DATASUS not providing the variables used in the study separately, which prevents performing the adjusted Odds ratio. Finally, it is also worth noting the limitations of the case-control study itself, which, due to the existence of confounding factors, cannot confirm the hypotheses made.

CONCLUSIONS

In summary, the findings suggest that preterm birth, cesarean birth, and ethnicity are associated with the occurrence of BAVMs in newborns. Further research is needed to understand the underlying mechanisms and to validate these associations. The results highlight the importance of prenatal and perinatal factors in the

development of BAVMs and may aid in identifying at-risk populations for targeted interventions and monitoring.

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