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ABSTRACT
Introduction. Brain vascular malformations (BVMs) are congenital lesions with evolutive properties that possess a considerable chance of causing intracranial hemorrhage. The most common types are arteriovenous malformations (AVMs), aberrant entanglements of deformed vessels that shunt blood from the arteries directly into the veins, and cavernous malformations (CMs), being mulberry-shaped sinusoid spaces filled with blood. The rate of hemorrhagic stroke varies between these two types of lesions, being the most common form of symptomatic presentation for AVMs, but a much rarer occurrence for CMs. The purpose of our pilot study was to test whether the incidence of intracranial hemorrhage from BVMs varies between seasons, as well as examining a possible causality for this event.
Material and methods. We performed a retrospective analysis on the cases of ruptured BVMs of the brain operated by the senior surgeon in our department between January 2008 and December 2019. We then divided the patients according to type of lesion and gender, based on the month of the year when their pathologies caused hemorrhagic stroke. We performed Pearson's chi square test to verify the

relationship between season and rate of rupture of AVMs and CMs, individual month and rate of rupture, season and gender, and individual month and gender.

Results. There were 87 ruptured vascular malformations, out of which 71 were AVMs and 16 were CMs. There were 51 males (40 AVMs, 11 CMs) and 36 females (31 AVMs, 5 CMs). The majority of hemorrhagic strokes occurred in the months of July (10 AVVMs, 2 CMs) and December (10 AVMs, 1 CM). We obtained a statistically significant correlation between the summer season and presentation with ruptured cavernous malformation, as well as the male sex and presentation with a ruptured AVM in December, whereas the female sex presented a correlation with ruptured AVMs in the month of March. We also obtained a correlation between the male sex and presenting with a ruptured vascular malformation of any kind in December, as well as the female gender and hemorrhagic stroke from any vascular malformation in the months January and August.

Conclusion. Despite promising statistical results, the relatively low number of cases may not be applicable to a larger patient population. It seems probable that meteorological conditions, especially extreme temperatures, might act as an additional risk factor for hemorrhagic stroke from vascular malformations, however these findings should be corroborated with supplementary case series from other centers, or a large prospective trial.

Introduction

Brain vascular malformations (BMVs) represent congenital aberrations of the cerebral blood vessels, having evolutive properties and a variable tendency to cause hemorrhagic stroke across its subtypes. The most common BMVs are arteriovenous malformations (AVMs), which consist of an entanglement of abnormal vessels that shunt blood from arterial feeders directly into one or more draining veins [4, 5, 10]. Hemorrhagic stroke stands as their most common form of symptomatic presentation, AVMs being also the leading cause of spontaneous intracranial hemorrhage in the young population. Cavernous malformations (CMs), also referred to as cavernomas, have a lower prevalence than AVMs, are mulberry-shaped sinusoid caverns filled with blood in various stages of hemolysis and are generally asymptomatic upon discovery [1, 2, 9]. Regarding symptoms, epilepsy is described as the most frequent for CMs, hemorrhagic stroke being slightly less common.

Spontaneous intracranial hemorrhage (ICH), or hemorrhagic stroke, is responsible for roughly 20% of all stroke types [15, 20]. Despite medical and surgical advancements, it remains a mortifying pathology with a mortality as high as 30%, as well as a strikingly elevated morbidity among survivors. The influence of seasonal change on the propensity of hemorrhagic stroke has been widely investigated across several areas of the world, although the results are inconsistent and continuously debated. The majority of such studies described a rise in the incidence of stroke throughout the colder months of the year and a decline in the warmer months [3, 11, 12, 22].

Since AVM and CM rupture depends on both acquired and environmental factors, it is reasonable to assume that meteorological factors may indeed contribute to this event. Nevertheless, our current comprehension of the individual environmental triggers is narrow at best. Aside from risk factors such as smoking, alcohol and drug consumption, and various comorbidities like arterial hypertension and diabetes mellitus, we believe it important to also tackle the added influence of seasonal variation in hemorrhagic stroke from these lesions. In the present study, we examine the seasonal rates of rupture from BVMs which were admitted in our hospital in a 12-year interval.

Materials and methods

We conducted a retrospective analysis on the cases of ruptured BVMs (AVMs and CMs) operated by the senior surgeon in our department (the third author) between January 2008 and December 2019. Patient data was gathered from the hospital internal electronic database (AtlasMed), patient observation forms, surgery registry and the clinical imaging study database. We then divided the patients according to gender, age, and the histological type of lesion, based on the month of the year when their pathologies caused ICH. Inclusion criteria were the imaging and pathological confirmation of the vascular malformation, the presence of intracranial hemorrhage upon admission, as well as the surgical removal of the lesion. Patients with BVMs that did not present with rupture, were not confirmed as either AVM or CM by the pathologist, did not have a visible BVM on imaging study, or that did not benefit from surgery in order to have a final diagnosis were excluded from the study. Using Microsoft® Excel for Mac, we made the appropriate value distribution graphs. We performed Pearson's chi square test to verify the relationship between season and rate of rupture of AVMs and CMs, individual month and rate of rupture, season and gender, and individual month and gender.

Results

From the total of 202 BVMs operated in the specified interval by our senior neurosurgeon, 87 had ruptured prior to admission, out of which 71 (81.61%) were AVMs and 16 (18.31%) were CMs. There were 51 males (58.62%, with 40 AVMs and 11 CMs, representing 45.98% and 12.64% respectively) and 36 females (41,38%, with 31 AVMs and 5 CMs, accounting for 35.63% and 5.75% of cases respectively). The majority of ICH occurred during the months of July – 12 BVMs or 13.79% (10 AVVMs or 11.49%; 2 CMs or 2.3%); followed by December – 11 BVMs or 12.64% (10 AVMs or 11.49%; 1 CM or 1.15%). The months of March and November both accumulated 10 BVMs each (11.49%), the former having a total of 9 AVMs (10.34%) and 1 CM (1.15%), whereas the latter amassed 7 AVMs (8.05%) and 3 CMs (3.45%). Figure 1 reveals the total number of cases presenting with ruptured AVMs and CMs across each month.

Using Pearson's Chi squared test, we first compared AVMs to CMs in respects to the season they were most likely to rupture and obtained obtained a statistically significant correlation between the summer season and presentation with ruptured CM (chi^2 value of 4.3291, $p<.05$). Moreover, when taking each month individually, we found a statistically significant correlation between August and ruptured CMs (chi^2 value of 4.2902, $p<.05$) No other associations were statistically significant for this step. Tables 1 and 2 show the all of the results emerging from this group of investigations.

Table 1. BVM Risk of Rupture According to Histological Type by Season and Period

season/ period	AVMs total/ month	CMs total/ month	chi^2 value	p value	Interpre-tation
Spring	19	1	1.9058	1.9058 >.05	Non-Significant
Summer	**17**	**8**	**4.3291**	**.037467 <.05**	**Significant**
Autumn	18	5	0.2336	.628903 >.05	Non-Significant
Winter	17	2	1.0018	.316884 >.05	Non-Significant
total	71	16			

AVMs, arteriovenous malformations; CMs, cavernous malformations

Table 2. BVM Risk of Rupture According to Histological Type by Month

month	AVMs total /month	CMs total /month	chi^2 value	P value	Interpretation
January	5	1	0.0128	.910048 >.05	Non-Significant
February	2	0	Could not be calculated		
March	9	1	0.53	.081428 >.05	Non-Significant
April	6	0	Could not be calculated		
May	4	0	Could not be calculated		
June	4	3	3.0362	.096427 >.05	Non-significant
July	10	2	0.0276	.868123 >.05	Non-significant
August	**3**	**3**	**4.2902**	**.038334 <.05**	**Significant**
Sept.	6	1	0.0855	.770012 >.05	Non-significant
October	5	1	0.0128	.910048 >.05	Non-significant
Nov.	7	3	0.2564	.612595 >.05	Non-significant
Dec.	10	1	0.7256	.394304 >.05	Non-significant
total	71	16			

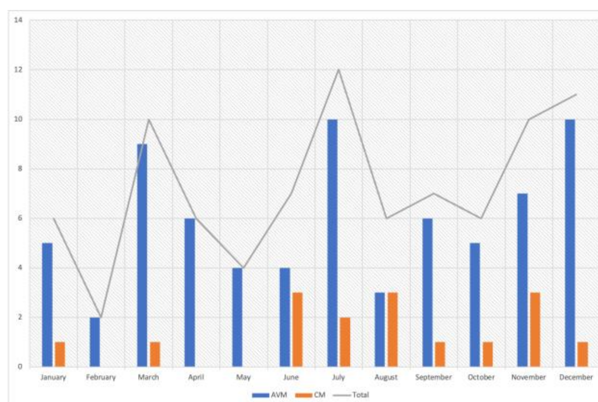

Figure 1. Diagram showing the cumulative incidence of ruptured brain vascular malformation based on type, according to calendar month. The ordinate shows the number of cases. AVM – arteriovenous malformation; CM – cavernous malformation.

Next, we took into account only the patients with ruptured AVMs and compared the two genders in respects to rupture risks during all the same months combined. Figure 2 shows the distribution of ruptured BVMs for both sexes across each month. We found a statistically significant correlation between the male sex and presentation with a ruptured AVM in the month of December (chi^2 value of 5.3617, p<.05), whereas the female sex was significantly correlated with ruptured AVMs in the month of March (chi^2 value of 4.8766, p<.05). Table 3 illustrates the complete results for this set of tests.

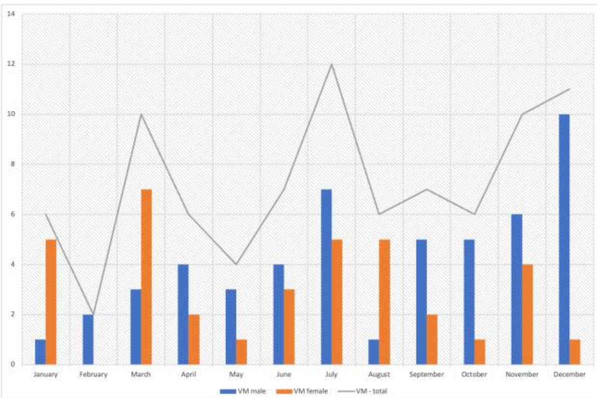

Figure 2. Diagram showing the cumulative incidence of ruptured brain vascular malformation based on patient gender, according to calendar month. The ordinate shows the number of cases. VM – vascular malformation.

Table 3. AVM Risk of Rupture According to Gender by Month

month	m. total /m.	f. total /m.	chi^2 value	P value	Interpre-tation
January	1	4	2.8874	.089277 >.05	Non-Significant
Feb.	2	0	Could not be calculated		
March	**2**	**7**	**4.8766**	**.027223 <.05**	**Significant**
April	4	2	0.2842	.593939 >.05	Non-significant
May	3	1	0.6001	.438524 >.05	Non-significant
June	1	3	1.6923	.193296 >.05	Non-significant
July	5	5	0.1901	.662852 >.05	Non-significant
August	1	2	0.6739	.411693 >.05	Non-Significant
Sept.	4	2	0.2842	.593939 >.05	Non-significant
Oct.	4	1	1.2243	.268522 >.05	Non-significant
Novem ber	4	3	0.002	963931 >.05	Non-significant
Dec.	**9**	**1**	**5.3617**	**.020584 <.05**	**Significant**
total	40	31			

AVMs, arteriovenous malformations; CMs, cavernous malformations

Last, we considered all BVMs, regardless of type, and again compared the hemorrhage risk for the two sexes along all of the same months. We discovered a statistically significant correlation between the male sex and a hemorrhage from a vascular malformation of any kind in December (chi^2 value of 5.412, p<.05), as well as the female gender and hemorrhagic stroke from any vascular malformation in the months January and August (chi^2 value of 4.6763 equally for each month, p<.05). No other significant associations could be established. The complete results of this step can be viewed in Table 4.

Table 4. Total BVM Risk of Rupture According to Gender by Month

month	m. total /m.	f. total /m.	chi^2 value	P value	Interpretation
Jan.	**1**	**5**	**4.6763**	**.030582 <.05**	**Significant**
Feb.	2	0	Could not be calculated		
March	3	7	3.8155	.05078 >.05	Non-significant
April	4	2	0.172	.678347 >.05	Non-significant
May	3	1	0.4637	.495889 >.05	Non-significant
June	4	3	0.0069	.934019 >.05	Non-significant
July	7	5	0.0005	.982633 >.05	Non-significant
Aug.	**1**	**5**	**4.6763**	**.030582 <.05**	**Significant**
Sept.	5	2	0.5148	.473064 >.05	Non-significant
Oct.	5	1	1.6225	.202741 >.05	Non-significant
Nov.	6	4	0.0089	.925001 >.05	Non-significant
Dec.	**10**	**1**	**5.412**	**.019999 <.05**	**Significant**
total	51	36			

Discussions

Within seasons themselves, the differences regarding the total number of ruptured AVMs was minor, whereas CMs tended to bleed more frequently during summer. The month of August showed a significantly higher relative frequency of ICH from CMs when compared to AVMs. Males showed a clearer tendency of BVM rupture in the month of December, whereas female patients had a higher propensity for ICH strictly from AVMs in March and from BVMs in general in January and August.

Currently, there is a scarcity of studies dedicated to the effects of weather on the incidence of hemorrhagic stroke, especially those from preexisting vascular lesions such as aneurysms, AVMs or CMs. To the extent of our knowledge, a single other article addresses the influence of seasons on the risk of spontaneous hemorrhage from AVMs [6]. Hakan et al. discovered that the highest incidence for AVM rupture in Istanbul ensued during winter, while its lowest occurred in summer, yet there were no proven statistical correlations to substantiate their results. With 78 ruptured malformations spread across 20 years, the difference between hemorrhagic stroke from AVMs was also higher for men during autumn and winter, although these were not as considerable the ones in our series. The authors concluded that aside from seasonal weather variations and individual risk factors such as alcohol consumption, the relative increase of the population during winter may also play a role in the upsurge of hemorrhagic stoke during winter. Regarding cavernomas, our literature search did not yield any articles discussing the effect of meteorological conditions on their rupture patterns.

Stroke mortality was proven to rise in holiday seasons, at least in certain regions such as in the Hiroshima Prefecture of Japan, or Taiwan [8, 14]. Yet the reason for this could not be accurately established due to a lack in more detailed clinical information like patient lifestyle, consumption of alcoholic beverages, smoking habits and so forth. In the Heilongjiang Province of China, the higher incidence of primary intracranial hemorrhage from hypertension within late spring and early autumn was attributed to the influence of daily mean ambient temperature, as well as its variation [22]. According to Zheng et al, unexpected changes in temperature, such as sudden drops during the hot weather or climbs during the cold, were met with an increase in the incidence of primary intracranial hemorrhage. Furthermore, in the same study, it was shown that the occurrence of SAH escalated throughout days with lower ambient temperature. On the other hand, in the Arab Peninsula, ischemic stroke was correlated with the higher amount of solar radiations specific for the summer season which could not be elucidated by physiological events indicative of either dehydration or hemoconcentration [19]. Therefore, the supposition that meteorological conditions influence the rates of stroke may not be far from true.

The peaks occurring at the months of March, July and December might suggest a propensity for BVMs to rupture whenever extreme temperatures are reached, or when there are large thermic variations. The more frequent hemorrhages could also be attributed to the stress related to the estival season or the festive holidays and their respective activities. The significant difference between genders within early winter remains intriguing and enigmatic, yet it cannot be entirely attributed to weather effects alone. One should also take into account the behavioral and socioeconomic aspects of the patients in the studied population. As such, there are clear trends of increasing alcohol consumption in the form of spirits and wine during late autumn and early winter in our country, possibly due to the lower temperatures occurring in this period, but also as a consequence of increased stress correlated with a progressively dynamic socioeconomic environment, as well as a widening poverty gap [16, 17]. Although probable interference from other seasonal exposures such as dietary changes, hypovitaminosis or viral infections cannot be excluded.

Studies have also tried to pinpoint specific individual meteorological factors which may influence the occurrence of spontaneous ICH. According to Neidert et al., relative humidity presented a strong fluctuation in the 2 days prior to ICH in patients with intracranial vascular lesions [15]. On the day of rupture relative humidity was significantly lower, suggesting that a low ambient humidity may promote hemodynamic and cardio-cerebrovascular conditions associated with ICH from these lesions. It has been shown that air humidity, along pollution and temperature, can influence the diameter of the brachial artery in patients with type 2 Diabetes mellitus, with higher temperature and humidity acting as vasodilators [21]. Conversely, it can be argued that a lower humidity may lead to vasoconstriction, although this might not suffice as a trigger for vascular malformation bleeds. Low humidity and air pressure cause an increase of blood viscosity via insensible water loss [7]. This in turn can also alter the autoregulation properties of arterial feeders in AVMs, as well as promote shear stress [13, 18]. Other reports revealed that low temperature is indeed a substantial risk factor for ICH, significantly correlated with the higher incidence of these occurrences during winter and early spring [11, 12]. Our findings are in line with these conjectures, showing that the increased incidence of ICH from vascular malformations during the colder months may not be coincidental. Nevertheless, it is as of yet unclear why so many our cases presented with rupture during summer and why the rate of rupture for CMs remains higher during the warmer months.

Nevertheless, these results should not be taken at face value. Statistical bias can occur from the relatively small number of cases from each individual month. We can, however, speculate that there is indeed a higher tendency for BVMs to rupture under certain environmental circumstances, such as high differences in temperature or atmospheric pressure. Yet determining these parameters retrospectively within a large timeframe can be difficult and more inaccurate than acquiring the same data upon hospital admission. Also, stress related to specific periods during the year may contribute to higher systemic blood pressure, ergo to an increase likelihood of these lesions to bleed. In order to resume and improve our research in the future, we intend to collect the meteorological data relevant to our patients on the same day in which they arrive. Another problem in our approach is that the total number of lesions is spread too thin across the twelve months, thus even a seemingly impressive frequency peak may actually denote a negligible difference. A larger case series, or a collaboration with other neurosurgical centers in this field, may solve this predicament in the future. Another limitation of this study is the lack of adequate meteorological data, particularly of the individual environmental factors such as temperature, relative humidity and air pressure in the days predating ICH. In a future continuation of this study, we propose a collaboration with the National Meteorological Association in order to obtain such relevant data. Despite this being a pilot study, we believe it could be further improved by enlarging the number of patients enrolled and by performing a multivariate analysis on the various individual meteorological, environmental, and geographical factors, as well as the individual characteristics of the patients and their BVMs.

Conclusions

According to our results, BVM rupture incidence is higher in the months of March, July and December. Moreover, CMs tend to rupture more frequently in the summer than AVMs. Males tend to present with rupture from AVMs during early winter, whereas females had ruptures in early spring. Despite the fact we achieved promising statistical results, due to the relatively low number of cases, our findings may not be applicable to a larger patient population. It may also be probable that our results are due to statistical bias, although we are optimistic regarding an actual relationship between meteorological conditions and an altered propensity of BVMs to rupture. This may also depend on geographical variations in risk factors. It seems likely that seasonal changes in the environment, especially extreme temperatures, might act as an additional risk factor for hemorrhagic stroke from vascular malformations, however these findings should be corroborated with supplementary case series from other centers, or a large prospective trial.

Conflicts of Interest

The authors have no conflicts of interest to report.

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