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ORIGINAL ARTICLE - VASCULAR NEUROSURGERY - ARTERIOVENOUS MALFORMATION

Affected health domains in patients with brainstem cavernous malformations

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Abstract

Background Brainstem cavernous malformations (CM) carry high risks of hemorrhage and neurologic morbidity. While much is published on physical effects of brainstem CM, very little is known about these patients' quality of life. This study aimed to assess the quality of life PROMIS-29 health domains of brainstem CM patients and identify quality of life predictors.

Methods This was a cross-sectional study of adult patients with at least one brainstem CM identified by advertising on the Angioma Alliance website and from our institutional CM registry. A web-based questionnaire was administered and included self-reported information about the patient, cavernous malformation, residual clinical symptoms, and treatment. In addition, patients filled out the PROMIS-29 (version 1.0). The PROMIS-29 has 7 health domains and is standardized against the general population. We defined impaired quality of life as at least one out of 7 abnormal domains and used a 1 standard deviation cutoff for abnormal. We verified clinical and radiographic data to self-reported data in 28.8% of patients.

Results A total of 104 patients (mean age of 46.5 ± 11.5 years; 77.9% females) were recruited. Most (82.7%) reported at least one symptomatic hemorrhagic event and 36.5% reported at least 1 surgical procedure. At least one abnormal PROMIS domain was present in 64.4% of patients with fatigue (34.6%), anxiety (35.6%), social (28.2%), and physical (27.9%) domains being the most common. Among patients with a Rankin Score of 0–2, 55% had at least one abnormal domain. Gait difficulty, but not age, sex, or surgery predicted impaired quality of life.

Conclusion More than half of patients with brainstem CM have impaired quality of life. Fatigue, anxiety, and social function, in addition to physical dysfunction, are common; practitioners should be aware of these concerns. PROMIS-29 provides additional information than modified Rankin Score and should be considered in clinical trials and when assessing treatment outcomes until a disease-specific outcome tool is available.

Keywords Cavernous malformation · Cavernous angioma · Quality of life · PROMIS-29

Introduction

Cavernous malformations are angiographically occult vascular malformations present in the brain, spinal cord, and, rarely, extra-axial nerve roots [4]. The most feared complication of these lesions is bleeding which can result in important morbidity. The risk of recurrent hemorrhage may be as high as 30% over 5 years in patients presenting with a symptomatic hemorrhage from a brainstem cavernous malformation. Significant deficit can persist in these patients as well as anxiety about when the next hemorrhagic event might occur. The modified Rankin Score has been the most commonly used functional outcome score in studies of patients with cavernous malformations with and without surgery. However, Modified Rankin Score has limitations and does not account for social and emotional effects of a disease.

Little is known about the quality of life of patients with brainstem CM. Most studies have been limited in numbers, single-center studies, and/or were surgical studies without a comparison group [1–3]. The PROMIS-29 tool has been assessed and validated in stroke, is easy to use, and is widely

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available [5, 6, 10]. The aim of this study was to assess the PROMIS-29 health domains of a cross-sectional population of patients with brainstem CM and determine what drives quality of life. In addition, we aimed to assess the proportion of patients with abnormal domains across modified Rankin groups.

Methods and materials

Study design An observational, cross-sectional study to analyze the quality of life among brainstem CM patients. This study was approved by the Institutional Review Board and is in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. This article does not contain any studies with animals performed by any of the authors.

Patient selection Patients with brainstem CM were recruited from the Mayo Clinic prospective cavernous malformation registry and through an advertisement on the Angioma Alliance website and the Mayo Clinic website. Adult patients (18 and older) were included if they had at least 1 brainstem CM. Patients were excluded if they were unable to access the web-based questionnaire. Patients were recruited from the first week of June 2018 until the last week of January 2019. Patients were also given the option to fill out a HIPAA form and provide either brain imaging or a brain imaging report to confirm the diagnosis and location of the CM.

Study tool Patients were asked to fill out a web-based questionnaire with 147 total questions. Basic information was gathered by self-report regarding their diagnosis (sporadic or familial form, multiple or single CM, and the specific location, if known), management (surgery, radiosurgery, and/or observation), functional, and work status. Patients reported any current, residual symptoms including difficulty in speaking, difficulty in swallowing, impairment of an extremity, numbness or weakness of the face, vision difficulty (loss, diplopia, ptosis), gait difficulty, hearing loss or tinnitus, dizziness, body pain, headache, mood changes, concentration issues, fatigue, and difficulty with sleep. In a subset of patients in whom medical records were accessible and HIPAA signed, the patient provided information was compared with the medical records to verify information provided. In addition to general information, the PROMIS-29 and several other (not reported here) quality of life tools were filled out.

For the current study, the PROMIS-29 (version 1.0) tool was used. This questionnaire was selected based on length, ease of administration (time), and prior use in neurological diseases including stroke [5, 6, 10]. Promis-29 includes physical function, anxiety, depression, fatigue, sleep, social role, and pain domains. The PROMIS-29 tool is standardized against the general population. Scores are standardized on the *T* scale with mean of 50 and standard deviation of 10. Higher scores designate more of what is being measured. In the case of depression, anxiety, fatigue, sleep, and pain, a higher score represents a worse outcome. However, in the case of physical function, and social function, a higher score represents a better outcome. We report the minimally clinically significant score (standard deviation of 5), often considered to be mild dysfunction, in addition to a more robust cutoff with a standard deviation of 10 [10]. We defined the primary endpoint of "impaired quality of life" as a patient with 1 or more PROMIS-29 domains in which the *T* score was greater than 1 standard deviation (or 10 points) from normal.

Data Analysis Descriptive statistics including means, standard deviations, and frequencies were utilized for patient characteristics and presenting symptoms. Associations of categorical variables were assessed using the chi-square or Fisher's exact test. Wilcoxon-rank-sum tests were assessed for continuous variables. Univariate and multivariate logistic regression models were assessed. Statistical analysis was done using JMP® (SAS Institute Inc., Cary, NC, 1989–2019) software. Two-sided P values < 0.05 were considered statistically significant.

T scores and the proportion of patients with 5 (mild)- and 10 (moderate to severe)-point standard deviations are reported. Impaired quality of life was defined as a patient who had at least one PROMIS-29 abnormal domain (more than 1 standard deviation).

Results

One hundred four patients (77.9% females; 91.3% white, 11.5% Hispanic) participated in this study (Table 1). The mean age of the patients at the time of the survey was 46.5 ± 11.8 years and the mean age at diagnosis of the CM was 39.8 ± 11.6 years. Sixty-one percent of patients had been diagnosed within the past 5 years. Twenty-one patients (20.2%) self-reported they had the familial form of CM, although 40 patients (38.5%) were unsure. The most common location of CM was the pons (67; 64.4%), followed by the medulla (17; 16.3%), and midbrain (5; 4.8%). Fifteen patients (14.4%) were unsure of the location within the brainstem and did not provide an MRI report for verification. The locations of 30 (28.8%) CM were verified using the brain imaging available to investigators. Patients were accurate with specific brainstem location in 26 of 30 patients (86.7%). Eighty-six (82.7%) of patients had one or more self-reported symptomatic hemorrhagic events and 46 (44.7%) reported 2 or more symptomatic hemorrhages.

Thirty-eight (36.2%) of the patients underwent surgery, 36.8% of which were more than 5 years prior to the survey.

Table 1 Demographic and clinical cohort data

Demographic	Total (%)
Age at time of survey	46.5 ± 11.8 years
Age at diagnosis	39.8 ± 11.6 years
Diagnosis less than 5 years	63 (60.6%)
Sex (female)	81 (77.9%)
Race (White)	95 (91.3%)
Ethnicity (Hispanic)	12 (11.5%)
Familial	Yes = 21 (20.2%) No = 43 (41.3%) Unsure = 40 (38.5%)
Clinical/radiologic information	
Location	Midbrain = 5 (4.8%) Pons = 67 (64.4%) Medulla = 17 (16.3%) Unsure = 15 (14.4%)
Number of symptomatic hemorrhages (subjective)	Never = 8 (7.8%) Once = 40 (38.8%) 2–3 times = 36 (35.0%) More than 3 times = 10 (9.7%) Unsure = 9 (8.7%) 1 missing data
More than 1 symptomatic bleed	46 (44.7%)
Treatment	
Surgery	38 (36.2%)
Radiosurgery	11 (10.5%)
Functional status	
Modified Rankin Score At time of diagnosis	0 = 8 (7.8%) 1 = 28 (27.2%) 2 = 25 (24.3%) 3 = 26 (25.2%) 4 = 13 (12.6%) 5 = 3 (2.9%) 1 missing data
Modified Rankin Score At time of the survey	0 = 10 (9.6%) 1 = 34 (32.7%) 2 = 36 (34.6%) 3 = 17 (16.3%) 4 = 7 (6.7%) 5 = 0 (0.0%)

Data verified with medical records in 30 (28.8%) of patients

Eleven patients (10.5%) underwent gamma knife therapy. At the time of diagnosis, 40.7% of the patients reported a modified Rankin Score greater than 2 while, at the time of the survey, only 23% of the patients have a modified Rankin Score greater than 2.

As a group, 67 patients (64.4%) had at least one abnormal domain using a cutoff of 1 standard deviation and 88 (84.5%) had at least one abnormal domain using the cutoff of 0.5 standard deviation. The proportion of patients with domain scores greater than one standard deviation from the general population ranged from 9.6% for sleep to 35.6% and 34.6% for anxiety and fatigue respectively (Table 2). On univariate analysis (Table 3), age, sex, prior surgery, and time from diagnosis did not influence impaired quality of life. However, most patients with any residual physical, cognitive, and mood deficits at the time of the survey did influence overall quality of life. A multivariate model assessed gait difficulty, lower cranial nerve dysfunction, pain, and fatigue/concentration. We could not include all positive univariate positive items due to small sample size. In this model, gait difficulty (OR 15.9; 1.5–162.5; $P = 0.0199$) remained significant.

We found 55.0% of those with self-reported modified Rankin Score of 0–2 had a least one PROMIS-29 domain abnormal (more than 1 standard deviation) and 88 (84.6%) had one or more domain abnormal using a 0.5 standard deviation cutoff (Table 4). In patients with higher modified Rankin Scores (3–4) compared with 0–2, the proportion of people with abnormal domains of physical function, fatigue, social, and pain function was higher. However, anxiety, depression, and sleep domains were similar in both groups. Figure 1 graphically shows the gradation of proportion of abnormal domain scores by modified Rankin Score.

Discussion

We report PROMIS-29 data for the first time on a cross section of patients with brainstem cavernous malformations, both treated and untreated. More than 60% of patients with brainstem CM have at least one abnormal health domain on PROMIS-29 using a conservative definition of 1 standard deviation from the normal general population, but almost 85% have at least one abnormal health domain if using the minimally clinically significant definition of 0.5 standard deviation. We found the most common domains affected included the following: anxiety, fatigue, physical function, and social function.

Cornelius and colleagues using the Short Form 36 (SF-36) in 60 patients with surgically treated CM similarly found that physical function and emotional role domains were poorer in brainstem CM ($n = 16$) compared with the general population and compared with non-brainstem CM ($n = 40$) [2]. They did not, however, find a difference in the mental health domain of brainstem CM compared witrh non-brainstem location or the general population. Another surgical study of brainstem CM patients only demonstrated decreased mental health scores compared with the general population, which improved after surgery [3].

In univariate analysis, almost any residual physical deficit resulted in impaired QOL as did reduction in concentration, sleep impairment, or fatigue. However, in multivariate analysis, gait dysfunction remained significant. We did not find surgery, age, gender, or number of symptomatic bleeds significant, although numbers limited our multivariate analysis. The latter finding was consistent with other studies suggesting no association between QOL and age, gender, or number of

Table 2 PROMIS-29 data—*T* scores and proportion of patients with abnormal scores

	Physical function (*T*+)	Anxiety (*T*−)	Depression (*T*−)	Fatigue (*T*−)	Sleep (*T*−)	Social (*T*+)	Pain (*T*−)
T score (Median and range)	45.3 22.9–56.9	55.8 40.3–48.1	51.8 41–71.2	55.1 33.7–75.8	50.5 32–73.3	48.9 29–64.1	52 41.6–75.6
Proportion with > 0.5 standard deviation	48 (46.1%)	54 (51.9%)	44 (42.3%)	57 (54.8%)	27 (26.0%)	45 (43.3%)	40 (38.4%)
Proportion with > 1 standard deviation	29 (27.9%)	37 (35.6%)	20 (19.4%)	36 (34.6%)	10 (9.6%)	29 (28.2%)	22 (21.1%)

(*T*+): Higher scores are favorable

(*T*−): Higher scores are unfavorable

hemorrhages [1]. No other studies assessed the residual neurologic deficits as predictors of quality of life.

We further found that patients with what is generally considered an "independent" or good outcome, modified Rankin 0–2 [9, 13], have abnormal domain scores (> 1 standard deviation) in anxiety (36.2%), fatigue (26.2%), depression (18.7%), pain (13.7%), physical function (12.5%), sleep (10.0%), and social (8.7%). Anxiety remains high (more than 30%) in both those with modified Rankin 0–2 and 3–4. We feel the PROMIS-29 better stratifies patient outcomes compared with the modified Rankin Score and should be considered in assessing outcomes in these patients. Other studies assessing ischemic stroke similarly show that the PROMIS-29 stratifies outcomes beyond using modified Rankin Scores [7, 8, 12]. Dukatz and colleagues showed in a prospective CM surgical study that additional information was provided by QOL scales (SF-36) performed before and after surgery compared with general outcome measures [3].

Previous studies assessing quality of life in patients with cavernous malformations have used the Karnofsky Performance Scale (KPS) [3], Patzold rating score [3], and the SF-36 [1–3]. The Patzold rating score is difficult to obtain and the Karnofsky performance score is primarily a physical function tool. SF-36 domains include the following: physical function, role physical, role emotional, social functioning, mental health, bodily pain, vitality, and general health. Both SF-36 and PROMIS-29 add additional information beyond modified Rankin Score, although neither are disease specific. For example, a change in physical function due to a broken leg could affect either of these scores as well. Currently, there are no disease-specific cavernous malformation quality of life tools.

We acknowledge that the best way to approach this would be a prospective study with quality of life surveys at designated time periods; however, it would take years to gather the appropriate data necessary. Our study utilized a web-based

Table 3 Univariate analysis of factors affecting "good" versus "impaired" QOL[a]

Factors	"Good QOL"	"Impaired QOL"	*P* value
N	37	67	
Age at time of survey	46.6 ± 13.3	46.3 ± 10.9	0.9810
Age at Diagnosis	41.1 ± 13.0	39.1 ± 10.8	0.5705
Sex (female)	26 (70.2%)	55 (82.1%)	0.1644
> 5 years post diagnosis	14 (37.8%)	27 (40.3%)	0.8058
Prior surgery	10 (27.0%)	27 (40.3%)	0.1759
Prior surgery > 5 years	3 (33.3%)	11 (47.8%)	0.4575
> 1 symptomatic hemorrhage	17 (45.9%)	29 (43.9%)	0.8442
Extremity dysfunction	3 (8.1%)	29 (43.3%)	0.0001
Vision	5 (13.5%)	27 (40.3%)	0.0046
Dizziness	7 (18.9%)	35 (52.2%)	0.0009
Sleep	2 (5.4%)	17 (25.4%)	0.0155
Lower cranial nerves[b]	6 (16.2%)	26 (39.3%)	0.0147
Any pain (headache and body pain)	5 (13.5%)	30 (44.8%)	0.0012
Impaired gait	1 (2.7%)	23 (34.3%)	0.0002
Impaired Mood/fatigue/concentration	7 (18.9%)	40 (59.7%)	< 0.0001

[a] "Impaired QOL" defined by 1 or more abnormal domains where abnormal is defined as greater than 1 standard deviation from the 50 (*T* score average for general population)

[b] Lower cranial nerves consisted of speech and/or swallowing dysfunction, face weakness or numbness, hearing loss (pontine and medullary cranial nerves)

Table 4 PROMIS-29 scores comparing modified Rankin Scores of 0, 1, 2 versus 3, 4, 5

	Rankin 0, 1, 2	Rankin 3, 4, 5	*P* value
At least one abnormal domain (> 1 STD)	44 (55.0%)	23 (95.8%)	0.0002
At least one abnormal domain (> 0.5 STD)	64 (80.0%)	24 (100.0%)	0.0200
Physical domain *T* score	48 (30.7–56.9)	32.7 (22.9–43.4)	< 0.0001
Physical domain > 0.5 STD	24 (30.0%)	24 (100%)	< 0.0001
Physical domain > 1 STD	10 (12.5%)	19 (79.2%)	< 0.0001
Anxiety *T* score	53.7 (40.3–81.6)	55.8 (40.3–67.3)	0.5726
Anxiety domain > 0.5 STD	39 (48.7%)	15 (62.5%)	0.2370
Anxiety domain > 1 STD	29 (36.2%)	8 (33.3%)	0.7935
Depression *T* score	49 (41–71.2)	54.8 (41–71.2)	0.0292
Depression domain > 0.5 STD	32 (40.0%)	12 (50.0%)	0.3845
Depression domain > 1 STD	15 (18.7%)	6 (25.0%)	0.5035
Fatigue *T* score	53.1 (33.7–75.8)	62.7 (43.1–75.8)	0.0012
Fatigue domain > 0.5 STD	39 (48.7%)	18 (75.0%)	0.0234
Fatigue domain > 1 STD	21 (26.2%)	15 (62.5%)	0.0011
Sleep *T* score	50.5 (32–73.3)	852.4 (32–73.3)	0.4858
Sleep domain > 0.5 STD	19 (23.7%)	8 (33.3%)	0.3476
Sleep domain > 1 STD	8 (10.0%)	2 (8.3%)	0.8081
Social *T* score	51.6 (29–64.1)	36.5 (29–49.8)	< 0.0001
Social domain > 0.5 STD	24 (30.0%)	21 (87.5%)	< 0.0001
Social domain > 1 STD	7 (8.7%)	18 (75.0%)	< 0.0001
Pain *T* score	49.6 (41.6–75.6)	56.35 (41.6–75.6)	0.0189
Pain domain > 0.5 STD	27 (33.7%)	13 (54.2%)	0.0714
Pain domain > 1 STD	11 (13.7%)	11 (45.8%)	0.0007

STD, standard deviation

survey which may exclude patients with the most severe disease as they may be unable to fill out a survey and those that were non-English speaking. Some patients are more motivated to fill out surveys about their health and others have found a difference in patient organizations versus clinical practice when assessing quality of life [11]. For example, the anxiety score may be higher due to the way we ascertained patients. We had a higher number of women participate. Clinical information was self-reported by the patient which could lead to errors in interpretation. We were, however, able to verify the provided data with medical records in nearly 30% of patients to reduce such bias. We noted that more than 1/3 of patients were unaware if they had the familial form of CM and thus unable to interpret whether this factor has influence across domains. We also relied on self-report of clinical hemorrhages. In patients where we could verify self report of hemorrhage, the patients were 100% accurate. Additional studies with more patients and verified clinical information would

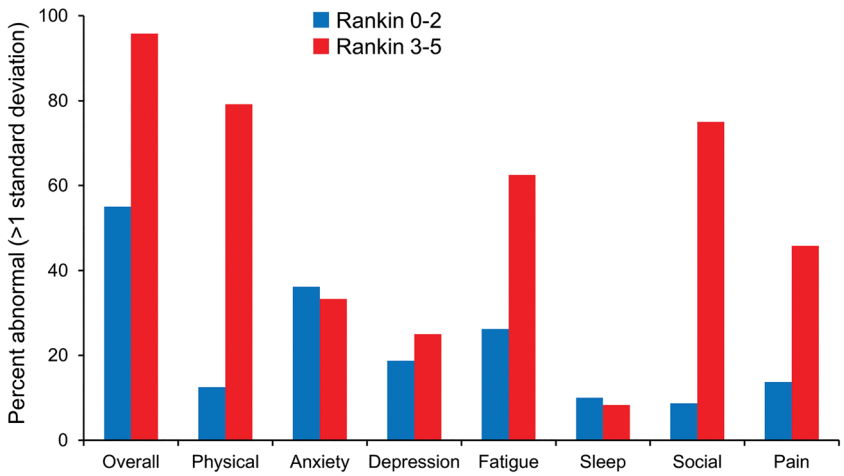

Fig. 1 PROMIS-29 domain scores by modified Rankin Score. The overall score refers to one or more abnormal domains

allow greater power and ability to perform more in depth multivariate analysis.

Conclusions

We found a high proportion of patients with brainstem cavernous malformations have impairment in anxiety, fatigue, social, and physical domains. This was true, even in patients with modified Rankin Scores of 0–2, which are considered "good" outcome. While the population was highly select and subject to bias, we do believe that the PROMIS-29 tool could add important information beyond modified Rankin Score when assessing these patients in clinical trials or assessing surgical outcomes until a disease-specific tool is available. In addition, the high rate of anxiety and fatigue should be addressed by practitioners during clinical encounters.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Mayo Clinic Institutional Review Board and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Statement on the welfare of animals This article does not contain any studies with animals performed by any of the authors.

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