Health-related quality of life in patients with untreated cavernous malformations of the central nervous system

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Background and purpose: To estimate health-related quality of life (HRQOL) in patients with untreated cavernous malformation of the CNS [cavernous cerebral malformations (CCMs)].

Methods: We performed a cross-sectional observational study on patients with CCMs admitted to our department from 1 November 2017 to 10 January 2020 using standardized interviews [short-form-36 questionnaire, hospital anxiety and depression score (HADS-A/D), CCM perception questionnaire]. Included criteria were diagnosis of an untreated CCM and information about the diagnosis in a specialized CCM consultation. Health-related quality of life (HRQOL) data were analyzed and compared to the German normal population. Uni- and multivariate analyses were carried out to identify variables with impact on outcome.

Results: Two hundred nineteen (93%) of 229 eligible patients were included. Mean age was 46.3 ± 14.7 (18–86) years; 136 (62%) were female. Ninety-eight (45%) patients presented with symptomatic hemorrhage (SH), and 17 (8%) with repetitive SH. Ninety-two (42%) patients were asymptomatic. Thirty-seven patients (17%) suffered from cavernoma-related epilepsy. Twenty-eight patients (13%) suffered from familial CCMs. Patients showed significantly decreased component scores and subdomain scores compared to the normal population, with effects ranging from small to large. This accounted largely also for asymptomatic patients (except for physical component score and main physical subdomains). Multivariate regression analysis confirmed impact of functional impairment on physical component score. HADS-A was significantly increased. HADS-A/D strongly correlated with mental component score and individual perception of the CCM.

Conclusions: Patients with the diagnosis of a CCM showed decreased HRQOL compared to the normal population even when not suffering functional impairment or neurological symptoms. Our data may function as benchmarks in evaluation of different (future) management strategies.

Introduction

Cavernous cerebral malformations (CCMs) are vascular malformations prone to intracerebral hemorrhage (ICH), with an estimated bleeding risk of 2.5%/year [1,2]. They comprise 10% to 15% of all intracranial vascular malformations [3]. Prevalence in the general population is approximately 0.5% [4]. CCMs occur in sporadic (80%) or a familial, autosomal-dominant (20%) form [1]. In the latter, oftentimes multiple CCM lesions are found, increasing in number throughout the patients’ lifetime. Clinical presentation is mostly

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seizures (oftentimes causing cavernoma-related epilepsy (CRE) [5]) or focal neurological deficits. However, 20% to 50% of CCMs are discovered incidentally, nevertheless carrying the risk of future hemorrhage [2,6]. With the widespread availability of magnetic resonance imaging (MRI) diagnostics, detection rates of (incidental) CCMs are increasing [7,8]. Current established treatment options for CCMs include surgical resection, which has been shown to be effective, as well as stereotactic radiotherapy, in which efficacy is still a matter of debate [9,10]. Overall, patients currently face a situation where indications for (future) treatment options are controversial, especially in patients with minor symptoms or asymptomatic CCM. [6,11], and influencing factors and mechanisms triggering symptomatic hemorrhage (SH) are only partly understood. The many pending uncertainties of both patients and practitioners have just recently been summarized [15].

However, whilst reporting standards [16] and all larger previous series mainly focus on occurrence/rate of SH and functional impairment, the important clinical parameter health-related quality of life (HRQOL) to estimate the burden of a disease has been nearly completely neglected in patients with CCM. Only few series [12,17–20], especially on postoperative HRQOL [12,19,20], exist.

Health-related quality of life is defined by the extent to which one’s usual or expected physical, emotional and social personal comfort is affected by a health condition or a treatment [21,22]. In clinical outcome research, HRQOL is seen as an important parameter in addition to functional outcome measures, and should also function as a reference value when indicating invasive or medical treatment in specific diseases [23,24]. Evaluation of HRQOL is particularly important in patients who have minor or no functional impairment (a majority of patients with CCM), as HRQOL does not necessarily correlate with functional outcome [25–27]. HRQOL has to be assessed independently [28].

Therefore, the aim of our study was to analyze HRQOL in a large cohort of patients with the diagnosis of an untreated CCM of the central nervous system (CNS). We also aimed to put the results in context with other psychological variables, assess potential influencing factors and compare results to the normal population.

Subjects/materials and methods

Study design and population

We performed a prospective cross-sectional study of all patients consecutively admitted to our department from 1 November 2017 to 10 January 2020 that fulfilled the below-mentioned inclusion criteria. A standardized interview was carried out [baseline medical information, socio-educational background, 36-item Short Form (SF-36) questionnaire, hospital anxiety and depression score (HADS-A/D), CCM-specific self-assessment questionnaire].

The study was conducted according to the principles expressed in the Declaration of Helsinki, and local ethics approval was obtained (review board identification 15-6636-BO). Informed consent was obtained from all participants. The study was performed according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) protocol.

Inclusion criteria

We included all patients aged 18 to 80 years with diagnosis of a so far untreated CCM and for that reason admitted to our specialized outpatient clinic in the given time period. The diagnosis was based on MRI data. All patients underwent general information about the diagnosis in a specialized CCM consultation by the same interviewer (P.D.).

Exclusion criteria

Patients who underwent an invasive medical treatment necessitating hospitalization within the 3 months prior to the interview were excluded. Patients with insufficient knowledge of the German language, as the surveys require sufficient language skills to produce a comparable result, were also excluded.

Data collection and survey

Clinical baseline data of patients and CCMs were obtained prospectively. In all patients, mode of presentation (occurrence of SH, CRE, asymptomatic) was assessed according to reporting standards [16]. Further baseline clinical data were obtained [sex, age at diagnosis, primary CCM location, multiplicity of CCMs, time between diagnosis/last CCM event (SH/seizure) and evaluation of HRQOL, known chronic disease, known psychiatric disease, current medication]. Familial disease was defined as multiplicity of CCM without associated developmental venous anomaly/positive genetic testing/know familial disease. The degree of disability was assessed using the modified Rankin Scale (mRS). An experienced neuroradiologist independently assessed radiological data. HRQOL was assessed by standardized direct interview using the German version of the 36-item Short Form.
The survey was conducted after the patients were carefully informed about the diagnosis by the consulting physician (P.D.). The SF-36 questionnaire addresses eight domains [physical functioning (PF), role physical, bodily pain (BP), general health perception, vitality, social functioning, role emotional, mental health and two component scores, physical health score (PCS) and mental health score (MCS)]. Age- and sex-matched data from a German population sample were used as a reference sample [29]. Additionally, we assessed the HADS-A/D score to evaluate symptom-based depression and anxiety. The questionnaire contains 14 questions to evaluate anxiety and depression. Furthermore, subjective burden of the diagnosis of CCM was evaluated by a self-assessment questionnaire by a modified visual analog scale (VAS). The scale ranges from 1 to 10 points, whereas 1 means no burden and 10 means maximal impairment by the diagnosis (for the VAS scale see Supporting Information data). Asymptomatic patients were further divided in those with valid reason to undergo MRI (CNS comorbidity, volunteer in MRI study, known familial disease, mild head trauma) and those with less valid reason (e.g. temporary single episode of headache unrelated to CCM, temporary single episode of mild balanced disorder unrelated to CCM) possibly indicating a rather overcautious/anxious basic posture.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 22 (IBM, Armonk, NY, USA). Nominal data were expressed as absolute number and valid percent, and continuous variables were expressed as mean and standard deviation. A Shapiro-Wilk test was used to test data for normal distribution. Additionally, histograms and Q-Q plots were used. We used parametric statistics for between-group comparison. We used the unpaired t test or Mann-Whitney U test for comparing continuous variables. For categorical variables, χ² or Fisher exact tests (expected frequencies < 5) were applied. Based on the German reference sample, a sex- and age-matched 1:1 case control sample was created. Comparison of mean values (SF-36 scores) was performed using the Student t test preceded by the Levene test. Effect size was reported using Cohen’s d.

To identify parameters with an impact on HRQOL in the complete participating cohort, bivariate correlation was performed. According to the variables character, Pearson, Spearman rho or Kendall tau-b tests were used. Clinically relevant and significant parameters (P < 0.05) were included in a linear regression analysis in terms of a stepwise model selection. All tests were two tailed (α = 0.05).

Results

Two hundred nineteen of 229 eligible patients (96%) were included in our study. Ten patients did not fulfill inclusion criteria or were not willing to participate. Mean age was 46.3 ± 14.7 (18–86) years, 136 (62%) were female and 93 (38%) were male. In 131 (55%) patients, a CCM was found without bleeding event. Ninety-eight (45%) patients presented with a first SH and 17 (8%) with more than one hemorrhage event. In 92 (42%) patients, the CCM was found coincidentally, as they were asymptomatic. Thirty-seven (17%) suffered from CRE. Twenty-eight patients (13%) showed familial disease with multiple CCMs. Fifty-five patients (25%) suffered from a chronic disease, 10 (5%) from a known psychiatric disease. Further information is found in Table 1.

SF-36 results in complete cohort, asymptomatic and symptomatic patients compared to the normal population

The SF-36 results and the age- and sex-matched German reference sample are shown in Table 2.

Table 1 Baseline characteristics of the cohort

| Characteristic              | Value       |
|----------------------------|-------------|
| Age, years (range)         | 46.3 ± 14.7 (18–86) |
| Sex, n (%)                 |             |
| Female sex                 | 136 (62)    |
| SH at presentation, n (%)  |             |
| Single SH                  | 98 (45)     |
| Repetitive SH              | 17 (8)      |
| Asymptomatic, n (%)        | 92 (42)     |
| Familial CCM, n (%)        | 28 (13)     |
| CRE, n (%)                 | 37 (17)     |
| Localization, n (%)        |             |
| Supratentorial             | 139 (64)    |
| Brainstem                  | 57 (26)     |
| Cerebellar                 | 12 (6)      |
| Spinal                     | 9 (4)       |
| mRS at presentation        |             |
| 0–1                        | 203 (93)    |
| 2                          | 10 (5)      |
| ≥3                         | 6 (3)       |
| Chronic disease, n (%)     | 55 (25)     |
| Psychiatric disease n (%)  | 10 (5)      |
| Time since diagnosis, month (range) | 20.4 ± 40.3 (0–268) |

CCM, cavernous cerebral malformations; CRE, cavernoma-related epilepsy; mRS, modified Rankin Scale; SH, symptomatic hemorrhage. Values are given as n (%). *In case of multiplicity we chose the symptomatic CCM as the significant location.
Compared to the age- and sex-matched German normal population, CCM patients (complete cohort) showed significantly decreased scores in all eight domains and in both component scores ($P < 0.05$). Forty-two percent (92/219) of the cohort showed a PCS two points lower than the mean score of the normal population. Fifty-four percent (119/219) showed such a decrease in the MCS. A two-point decrease is regarded as clinically and psychosocially relevant to patients [30,31]. Subgroup analysis revealed that asymptomatic patients also showed significantly decreased SF-36 values except for PCS, BP and PF compared to the normal population. Symptomatic CCM patients show decreased HRQOL in all domains and component scores accordingly. Specific values for brainstem versus non-brainstem CCM patients are found in Table S1. Further subgroup analysis results are also shown in Fig. 1. The subgroup analysis of asymptomatic patients (‘valid’ reason to undergo an MRI versus less valid reason) is found in Table S2. We found solely significant differences for the subdomain pain (BP) and the physical component score (PCS).

### Anxiety and depression scores, VAS scores

Mean HADS-D score was 4.26 ± 3.8 (0–20), mean HADS-A score was 7.0 ± 4.3 (0–20) and mean VAS was 4.9 ± 2.3 (1–10). Mean HADS-A score was significantly increased compared to the German normal population [29]. A high proportion of patients also showed increased levels of anxiety [8+, HADS-A, 86 (39%)] when compared to the normal population (20%) [29]. Depression scores showed increased values [8+, HADS-D, 42 (19%)] in a proportion of patients comparable to the normal population (21%) [29]. VAS score was > 5 in 89 (41%) patients. Bivariate correlation showed significant correlation of VAS, HADS-A and HADS-D (coefficient: 0.406, 0.369, $P < 0.0001$, $P < 0.0001$) in the overall cohort. When comparing asymptomatic and symptomatic patients, mean values of HADS-A and HADS-D showed no significant differences ($P = 0.9$ and $P = 0.4$), whereas VAS scores were significantly different ($P < 0.001$). The distribution of MCS, PCS, HADS-A and HADS-D scores across VAS categories is visualized in Fig. 2.

### Table 2 SF-36 results of the complete cohort

| SF-36 scale | Mean | $P$ | Cohen’s $d$ | Cohen’s $d$ effect$^a$ | Reference sample, $n = 219^b$ |
|-------------|------|-----|-------------|-----------------------|-----------------------------|
| Physical health subdomains |       |     |             |                       |                             |
| PF          | 83.6 ± 22.6 | 0.017 | 0.23 | Small | 88.3 ± 18.1 |
| RP          | 66.9 ± 40.3 | <0.0001 | 0.55 | Medium | 86.4 ± 29.3 |
| BP          | 74.5 ± 28.7 | 0.014 | 0.24 | Small | 80.8 ± 24.3 |
| GH          | 61.9 ± 21.5 | <0.0001 | 0.43 | Small | 70.2 ± 16.8 |
| VT          | 51.8 ± 20.7 | <0.0001 | 0.61 | Medium | 63.3 ± 16.9 |
| Mental health subdomains |       |     |             |                       |                             |
| SF          | 73.9 ± 24.9 | <0.0001 | 0.71 | Medium | 89.2 ± 17.4 |
| RE          | 66.2 ± 41.7 | <0.0001 | 0.80 | Large  | 92.8 ± 21.8 |
| MH          | 64.9 ± 19.8 | <0.0001 | 0.41 | Small  | 72.2 ± 15.6 |
| Component scores |       |     |             |                       |                             |
| PCS         | 48.9 ± 10.1 | 0.007 | 0.25 | Small  | 51.3 ± 8.8 |
| MCS         | 43.9 ± 11.2 | <0.0001 | 0.73 | Medium | 51.0 ± 7.9 |

BP, bodily pain; GH, general health perception; MCS, mental health score; MH, mental health; PCS, physical health score; PF, physical functioning; RE, role emotional; RP, role physical; SF, social functioning; SF-36, 36-item Short Form; VT, vitality. $^a$0.2 small, 0.5 medium, 0.8 large effect. $^b$Age- and sex-matched sample from the German reference cohort.

Compared to the age- and sex-matched German normal population, CCM patients (complete cohort) showed significantly decreased scores in all eight domains and in both component scores ($P < 0.05$). Forty-two percent (92/219) of the cohort showed a PCS two points lower than the mean score of the normal population. Fifty-four percent (119/219) showed such a decrease in the MCS. A two-point decrease is regarded as clinically and psychosocially relevant to patients [30,31]. Subgroup analysis revealed that asymptomatic patients also showed significantly decreased SF-36 values except for PCS, BP and PF compared to the normal population. Symptomatic CCM patients show decreased HRQOL in all domains and component scores accordingly. Specific values for brainstem versus non-brainstem CCM patients are found in Table S1. Further subgroup analysis results are also shown in Fig. 1. The subgroup analysis of asymptomatic patients (‘valid’ reason to undergo an MRI versus less valid reason) is found in Table S2. We found solely significant differences for the subdomain pain (BP) and the physical component score (PCS).

### Figure 1 Short Form-36 (SF-36) domains and component scores. A comparison between the reference group and subgroups of the cohort. Asy, asymptomatic; BP, bodily pain; BS, brainstem; GH, general health perception; MCS, mental health score; MH, mental health; Mult, multiple; PCS, physical health score; PF, physical functioning; RE, role emotional; RP, role physical; RS, reference sample; SF, social functioning; VT, vitality.

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Bivariate correlation and linear regression of HRQOL results

Bivariate correlation was performed for component scores MCS and PCS. We performed correlation with clinical and psychological parameters. Results are found in Table 3. Significant variables were adjusted for in two multivariate regression models: a clinical and psychological model. $R^2$ scores for the models were as follows: clinical model: PCS and MCS 0.214 (21%) and 0.062 (6%), respectively. Psychological model: PCS and MCS 0.155 (16%) and 0.488 (49%), respectively. Further results are found in Table 3.

Time since diagnosis

As this study is cross-sectional, patients were examined at different time-points since the diagnosis or their last SH or seizure due to CRE (defined as the last event). In bivariate analysis, the timely relation to the last event was significantly correlated with component scores, namely an increase of scores with increasing timely distance to the event. In the multivariate analysis, this correlation stayed a trend only. Figure 3 shows scattered plots that visualize this correlation. The low $R^2$ scores (0.005, 0.017) indicate that only a small proportion of the variance was explained by the time since diagnosis/last event.

Discussion

We present the largest cross-sectional study on HRQOL of untreated CCM published so far. We included 96% of a consecutive series of 229 patients referred to our department for the first time during a 26-month period and compared results to the German normal population. Our cohort shows the typical characteristics of CCM patients when compared to population-based cohorts [7] and other tertiary referral center cohorts/surgical series [13,32], and can therewith be regarded as a representative sample. All data were assessed according to reporting standards [16]. Our results are of clinical importance, as HRQOL and other psychological data of untreated CCM patients are barely available so far [17,18]. Such data are necessary to function as benchmarks when evaluating surgical or medical treatment options for CCM [12]. This is even more important, as indications for (radio-) surgical treatment of CCM still remain controversial [6,11]. The same accounts for the newly discovered potential drug candidates that will probably be tested in randomized controlled trials in the next decade [14]. Finally, the basic disease burden of CCM patients, especially in asymptomatic patients (mainly suffering from fear of a potential bleeding), has not yet been evaluated and defined in such detail. In this regard, HRQOL and other psychological
parameters play an important role, as they have the potential to reflect disease burden beyond mere functional impairment or hemorrhage/seizure rates [16,25].

The main results of our study were significantly decreased mean component scores and subdomain scores in the overall cohort compared to the normal population. The effects ranged from small to large, depending on the specific domains. To note, a decrease of two or more points in component scores (accounting for 42% and 54% of patients in our cohort for PCS and MCS, respectively) and five or more points in subdomains are regarded as clinically and psychosocially relevant to patients [30,31].

Moreover, even asymptomatic patients showed significantly decreased scores, mainly in mental health subdomains and mental component score. This may reflect the impact of the mere diagnosis of a vascular lesion with the potential to cause ICH. Supporting this hypothesis, anxiety levels as measured by HADS-A were also increased in the cohort when compared to the normal population. With the utilization of the VAS we tried to distinguish these effects from baseline anxiety disorders independent from the CCM. Univariate and multivariate analysis suggested that decreased HRQOL (accordingly mainly mental component score) and increased anxiety and depression levels were strongly correlated with the patients’ own perception of the CCM as a threat (Fig. 2). The strong $R^2$ of the psychological regression model for MCS (49%) is also in support of this correlation. In this regard, it is a criterion for data validity and consistency that all interviews about diagnosis and nature of CCM were performed by the same interviewer in a standardized way. However, longitudinal data will be necessary to finally confirm this hypothesis (data collection ongoing). The comparison of asymptomatic patients with valid and less-valid reasons to undergo an MRI also did not lead to an additional gain of information in this respect. As expected, asymptomatic patients with valid reasons showed comparable HRQOL compared to those with less-valid reasons, except for significantly lower values of subdomain BP score and the PCS score. As to be expected, the PCS score was in strong correlation with the patients’ functional condition as measured by the mRS.

We also observed a trend toward an increase of HRQOL component scores with increasing timely distance to the CCM diagnosis or the last CCM-related event (SH/seizure) in the univariate analysis. This trend was stronger for the MCS. Clinically, it may reflect two effects: the typical resolving of neurological symptoms after a SH, which is seen in the majority of patients with moderate SHs (PCS) [33] and a hypothesized coping with the disease going along with a longer symptom-free time-period (MCS). In our study, regression analysis did not clearly confirm this trend. Further longitudinal data will also be necessary in this regard.

Few studies evaluating HRQOL in CCM exist so far: Cornelius et al. [19] and Dukatz et al. [20] evaluated HRQOL in patients who underwent surgery of brainstem or non-brainstem CCMs. Both reported increasing (only 24 patients with pre- and post-operative scores) scores or postoperative scores comparable to the normal population in the long-term follow-up. Kumar et al. [18] reported on 56 untreated brainstem

### Table 3 Bivariate and multivariate analysis for MCS and PCS

| Variable                      | PCS | Coefficient | P    | Coefficient | P    |
|-------------------------------|-----|-------------|------|-------------|------|
| **Bivariate analysis**        |     |             |      |             |      |
| **Clinical parameters**       |     |             |      |             |      |
| Multiple CCM                 | −0.163 | 0.016 | 0.038 | 0.580 |     |
| CRE                          | 0.047 | 0.493 | −0.026 | 0.705 |     |
| Asymptomatic                 | 0.118 | 0.083 | 0.023 | 0.740 |     |
| mRS                          | −0.444 | <0.0001 | −0.122 | 0.071 |     |
| Brainstem location            | −0.105 | 0.122 | −0.035 | 0.605 |     |
| Age                          | −0.154 | 0.023 | −0.005 | 0.941 |     |
| Sex                          | −0.070 | 0.304 | −0.007 | 0.919 |     |
| SH                           | −0.177 | 0.099 | −0.097 | 0.244 |     |
| Repetitive SH                | −0.191 | 0.005 | −0.079 | 0.244 |     |
| Time since diagnosis          | −0.109 | 0.021 | −0.124 | 0.009 |     |
| Chronic disease              | −0.126 | 0.064 | −0.174 | 0.010 |     |
| Psychiatric disease          | −0.022 | 0.745 | −0.189 | 0.005 |     |
| **Psychological parameters** |     |             |      |             |      |
| HADS-A                       | −0.251 | <0.0001 | −0.603 | <0.0001 |     |
| HADS-D                       | −0.392 | <0.0001 | −0.649 | <0.0001 |     |
| VAS                          | −0.178 | 0.008 | −0.403 | <0.0001 |     |
| **Multivariate analysis**     |     |             |      |             |      |
| **Model 1: clinical parameters** |     |             |      |             |      |
| Multiple CCM                | −3.257 | 0.092 | n/a   | n/a   |     |
| mRS                         | −5.556 | <0.0001 | n/a   | n/a   |     |
| Age                         | −0.050 | 0.244 | n/a   | n/a   |     |
| SH                          | 1.001 | 0.467 | n/a   | n/a   |     |
| Repetitive SH               | 0.149 | 0.950 | n/a   | n/a   |     |
| Time since diagnosis         | 0.004 | 0.812 | 0.033 | 0.073 |     |
| Chronic disease             | n/a  | n/a   | −3.081 | 0.097 |     |
| Psychiatric disease         | n/a  | n/a   | −7.696 | 0.051 |     |
| **Model 2: psychological parameters** |     |             |      |             |      |
| HADS-A                      | −1.064 | <0.0001 | −1.248 | <0.0001 |     |
| HADS-D                      | −1.064 | <0.0001 | −1.248 | <0.0001 |     |
| VAS                         | −0.168 | 0.577 | −0.642 | 0.014 |     |

CCM, cavernous malformation of the CNS; CRE, cavernoma-related epilepsy; HADS-A, hospital anxiety and depression score A; HADS-D, hospital anxiety and depression score D; MCS, mRS, modified Rankin Scale; PCS, physical health score; SH, symptomatic hemorrhage; VAS, visual analog scale. Significant $P$ values are in bold type.
CCMs using the PROMIS-29 (Patient-Reported Outcomes Measurement Information System) questionnaire. In accordance with our findings, they described impairment in anxiety, fatigue, social and physical domains even in patients without functional impairment. However, the reported cohort was highly select. Bicalho et al. [17] presented SF-36 and EuroQol 5 (EQ-5D) analysis in 49 patients with untreated CCMs. They found decreased scores in pain, vitality and general health perception domains. To note, 65% of patients in this cohort suffered from a familial disease, which is way above the typical 15% to 20% proportion [32], also making the cohort highly select. Rinkel [12] used EQ-5D-SI data from a survey of both treated and untreated CCM (n = 140) patients to estimate quality-adjusted life years for a Markov model calculation for treatment decisions on CCMs. Due to fragmentary baseline data of the patients, no further analysis of HRQOL was possible. Most importantly, authors stated that more robust data on HRQOL are necessary to evaluate treatment strategies.

Our data also have shortcomings: (i) SF-36 is not a disease-specific but a generic instrument to assess HRQOL. Generic instruments are potentially less responsive to clinically important changes in health in a specific patient population [12]. However, no disease-specific instrument for CCM exists so far. (ii) The perception of and potential coping with a diagnosis is highly individual. Also, it is dependent on the form and content of provided information by the practitioner. Information on the diagnosis of a CCM and potential treatment options may internationally, and even nationally, widely vary. In our clinic, having a specialized outpatient clinic and a high amount of yearly (new) admissions (approximately 100), and a low surgical treatment rate (<15% in the observation period), we have established a rather conservative policy toward invasive treatment, emphasizing the usually very benign natural history of CCMs. Undoubtedly, the communication of the diagnosis strongly influences the further coping of the patient. (iii) Psychiatric diseases were known in 5% of our cohort. We have not specifically screened the patients for unknown psychiatric diseases that may interfere with HRQOL. (iv) Cross-sectional data have natural limitations that can only be clarified by longitudinal data assessment. Such data collection is currently ongoing.

We present the largest observational study on HRQOL in patients with untreated CCM published so far. Patients showed decreased HRQOL compared to the normal population even when not suffering functional impairment or neurological symptoms. Our data may function as benchmark in evaluation of different (future) management strategies.

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Disclosure of conflicts of interest
The authors declare no financial or other conflicts of interest.

Data availability statement
The data that support the findings of this study are available from the corresponding author upon reasonable request.
Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Quality of life in brainstem vs. non-brainstem location.

Table S2. Quality of life in the subgroup of asymptomatic patients divided into patients with high or low valid MRI reason.

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