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Quality of life in patients with vascular malformations outside the central nervous system – comparison with the general Norwegian population.

Summary

Purpose

The aim of this study was to assess Health-Related Quality of Life (HRQoL) in a population of patient with vascular malformations outside the central nervous system (CNS), and to compare the results with data from a national reference population.

Methods

In total, 111 consecutive patients above 14 years of age and referred for the first time to the national vascular malformation center from September 2011 to December 2012 were included. HRQoL was assessed using the Short-Form 36-item questionnaire (SF-36), which is a validated questionnaire with eight domains, covering both physical and mental aspects of HRQoL. The results were compared with national reference values. Possible association between HRQoL and selected demographic- and clinical variables was analyzed using linear regression.

Results

The sample consisted of 47 males (42.3%) and 64 women (57.7%). The median age was 27 years (range 14-63). Ninety-six patients (86.5%) were diagnosed with venous malformations and nine patients (8.1%) with arteriovenous malformations. Six patients had other types of malformations (9%). The patients had significantly lower SF-36 scores in all domains, except for General health, compared to the general population. There was a significant association between muscular involvement and lower SF-36 scores, in the physical domains *Bodily pain* and *Role limitation due to physical problems*.

Conclusions

Our data suggest that patients with vascular malformations outside the CNS have impaired quality of life, when compared to the general population. Muscular involvement seems to be associated with worse HRQoL, in the physical aspects.

Key-words: Health-Related Quality of Life, Vascular Malformations, Mental health, Musculoskeletal pain.

Introduction

Vascular malformations constitute a wide spectrum of lesions that lead to varying degree of morbidity. Epidemiological data are lacking, but the estimated prevalence of vascular malformations in a Hungarian population was 1.2%. No sex predilection was reported. (1). The disorders may cause considerable physical and mental discomfort, which may lead to impaired quality of life.

Vascular malformations are present at birth and grow proportionally with the patient. They are divided into capillary, lymphatic, venous and arteriovenous malformations, or a combination of the above (2). Venous malformations are the most common type, constituting 2/3 of all vascular malformations (3). The vast majority of vascular malformations are considered to represent somatic mutations; hence they may occur anywhere in the body (4) . The clinical presentation is varied and may depend on the type or size of malformation, the anatomical location and which tissue layers are involved. The most common symptom of vascular malformations outside the central nervous system (CNS) is pain due to thrombosis, stasis and swelling, as well as mass effect and local infiltration. Hemorrhage may occur, sometimes causing significant impairment (5). Vascular malformations may be cosmetically disfiguring, especially in the head and neck region (6-8).

Current treatment options comprise both conservative methods like compression garments, endovascular interventional techniques and surgery. Method of choice depends on a number of aspects, among them the type of malformation, localization and severity of symptoms (5, 9, 10). According to recent publications, also medical treatment has shown promising results (11, 12).

When evaluating treatment effect, radiological imaging could provide valuable information in some cases, but the determining factor of treatment success should primarily be based on symptomatic improvement and patient satisfaction (13). To better understand how the patients are affected by the malformations, and to evaluate treatment outcome, assessing Health Related Quality of Life (HRQoL) could provide valuable information. However, only a few studies have been published on the topic, with varied study design and results, and often with few patients included (6-8, 14-17).

The primary aim of this study was to assess quality of life in patients with vascular malformations referred to a national treatment center and compare the results with quality of life reference data from a sample from the Norwegian general population. The secondary aim was to identify demographic and clinical characteristics associated with quality of life in a group of patients with vascular malformations.

Patients and methods

The study was conducted at Oslo University Hospital, Rikshospitalet, which is the national referral center for vascular anomalies in Norway. The center is organized as a multidisciplinary clinic, including the following specialists: plastic surgeons, interventional radiologists, ENT-surgeons, orthopedists, pediatricians, geneticists, dermatologists and ophthalmologists. The department of plastic surgery is the head department, receiving the majority of patients with vascular malformations. Our inclusion criteria were 1) patients above 14 years of age with a suspected diagnose of vascular malformation and 2) referred for the

first time to our national treatment center for diagnostic workup and treatment and 3) a confirmed diagnose of vascular malformation after diagnostic workup. According to a publication by Ware (18), SF-36 is valid for persons aged 14 years and above, which is why this age cut-off was chosen. Between September 2011 and December 2012, 127 consecutive patients were asked to participate. 116 out of 127 patients accepted inclusion, of which five were excluded after ruling out the diagnosis vascular malformation. Written informed consent was obtained from all patients and the study was approved by the local ethics committee.

Demographic data were registered. Diagnostic workup was based on clinical examination, ultrasound and MRI, as described in previous publications (10, 19). In 101 patients, we performed MRI with dynamic angiography and in eight patients MRI without angiography. The following MRI data were evaluated: type of malformation, anatomical location, tissue layer involved and margins. In two patients, no MRI was performed; they presented with a small venous malformation in the lip and finger, respectively, and ultrasound was regarded as the diagnostic modality. Twenty-two patients underwent conventional angiography under the suspicion of having an AVM.

Quality of life assessment

Before diagnostic work-up, all patients were asked to fill in the SF-36 questionnaire which is one of the most widely used tools in HRQoL measures (20). SF-36 is developed from the Medical Outcomes Study (MOS) that was partially designed to develop practical tools for monitoring patient outcomes (21). SF-36 is not disease specific and consists of eight domains with multi item scales; *Physical functioning, Role limitations due to physical problems, Bodily pain and General health* provide a measure of physical aspects of HRQoL, whereas *Vitality, Social functioning, Role limitations due to emotional problems and Mental health* provide a measure of mental aspects. The items and scales were scored in three steps, according to the SF-36 algorithm described by Ware (22). First, ten of the items were

recoded, then raw scale scores were computed, and finally the raw scale scores were transformed into a 0-100-point scale, where the higher values indicate better quality of life.

Reference population

SF-36 was validated and translated into Norwegian in 1998 by Loge et al (23), and we used the translated SF-36 version 1 in this study. The same group published normative data for SF-36 in the Norwegian population in 1998 (24). Updated data was published in 2017 (20) and was based on a representative sample from the general Norwegian population (n=2107, median age 57 years (range 18-79), 54.3 % male, 44.7 % female).

Statistical methods

Continuous data were described with mean and standard deviation (SD), categorical data with counts and percentages. Crude differences concerning all the domains of SF-36 between the patients and the general population were analyzed using t-tests as all the outcome variables were considered normally distributed. To adjust for possible confounding with age and gender, we fitted multiple linear regression models.

Further, to identify possible associations between selected variables and HRQoL in our patient sample, we fitted multiple linear regression models. The results are expressed as regression coefficients (B) with 95% confidence intervals (CI). The following variables were analyzed: gender, age, type of malformation (high flow vs. low-flow), anatomical location (head and neck vs. trunk/extremity), tissue layer involved (subcutaneous involvement vs. muscular/bone involvement), and margins (well defined vs. ill-defined).

P-values <0.05 were considered statistically significant. All tests were two-sided. All analyses were conducted using SPSS version 25.

Results

The sample consisted of 47 males (42.3%) and 64 women (57.7%), median age was 27 years (range 14-63). There was a statistically significant difference in mean age between the patient cohort (31.0 years) and the reference population (55.5 years). The gender distribution was similar in both groups. The demographic and clinical data are summarized in table 1.

In univariate analyses, we found lower mean SF-36 scores in the patient cohort than the reference population for all domains, and the differences were statistically significant, except for *General health*. The most pronounced difference was seen in *Role limitation due to physical problems*, see table 2.

In a multivariate analysis adjusting for age and gender, the differences in SF-36 scores between the groups remained statistically significant for all domains, except for *Mental health* and *Vitality*. For *General health*, the difference turned out to be statistically significant. The most pronounced difference between the patients and the reference population was revealed for *Physical functioning* and *Role limitation due to physical problems,* were the patients had lower average scores of 17.2 and 31.6 points, respectively. The smallest difference was estimated for *Mental health*, were the patients scored 1.8 points lower. The results are summarized in table 3.

In the patient cohort and in a multivariate analysis, only associations between SF-36 score and the variables age and muscular/bone involvement remained statistically significant when adjusted for gender, type of malformation, anatomical location and margins. Higher age was associated with lower SF-36 scores in the physical domains *Physical functioning*, *Bodily pain* and *General health* and in the mental domain *Role limitation due to emotional problems*. Muscular/bone involvement was associated with lower SF-36 scores in the *Role limitation due to physical problems* and *Bodily pain* domains. No other demographic or clinical characteristics were significantly associated with HRQoL, for details, see table 4.

Discussion

The present study demonstrated that our patients had lower mean SF-36 scores than the Norwegian general population, for almost all the domains. The result suggests that patients with vascular malformations older than 14 years of age have impaired HRQoL, and both physical and mental aspects of HRQoL seem to be affected. The data was age-adjusted because of the reported association between higher age and higher SF-36 scores in the *Vitality*, *Mental health* and *Social functioning* domains in the reference population (20). When adjusted for age, our patients scored lower in all domains, except *Vitality* and *Mental health*. Interestingly, our data did not reveal any association between gender and changes in SF-scores.

In our patient cohort, higher age was associated with lower SF-36 scores mainly in the physical domains. Malformations involving muscles or bone were associated with lower SF-36 scores in the physical domains *Role limitation due to physical problems* and *Bodily pain*. This may indicate that patients with intramuscular lesions are physically more severely affected, and could be important knowledge when considering treatment indications. The majority of these patients are young and involved in physical activities at the time of diagnosis, which may explain the significant quality of life impairment in the physical domains. It is crucial that these patients are thoroughly evaluated regarding treatment options and –effect.

Previous studies have shown that malformations in the head and neck region may be cosmetically disfiguring (7, 8), and thus we anticipated head and neck malformations to be associated with lower SF-scores in the mental domains, however no such association was found. Patients with facial port-wine stains (PWS) were not included in our study. Facial PWS is usually diagnosed in infancy, and the follow-up is organized by the local hospital or the general practitioner. If facial PWS is related to a syndrome, the follow-up is organized by the department of pediatrics in our hospital. In cases of cosmetically disfiguring lesions, the patients may be treated by local dermatologists. Consequently, no patients above 14 years of age with facial PWS were referred to our clinic for diagnostic workup and treatment in the

inclusion period. Hagen et al. (25) found impaired quality of life in 244 patients with facial PWS, with the emotional domain most significantly influenced. Including this patient group in our study could have influenced the results. Furthermore, some patients with specific head- and neck symptoms may have been referred to the ENT-department, without being in contact with the vascular malformation unit, and possibly they were missed in the inclusion process. However, we believe this to be true only for a very small number of patients. With regards to mental health, the head and neck patients in our cohort were no more affected than other patients, thus exclusion of such patients is not likely to introduce any biases.

Association between sleeping disorders and HRQoL was not assessed in our cohort of head and neck patients. Durr et al. (26) found lower quality of life scores and a higher incidence of sleeping disorders in patients with head and neck malformations than in patients with vascular malformations in other locations. However, quality of life in this study was assessed in a pediatric population (mean age 7.3 years) with the obstructive sleep apnea-18 item questionnaire, and the results are not applicable to our patient population. Nevertheless, there could be an association between sleeping disorders and HRQoL also in adolescents and adults, and this should be analyzed in future studies.

No statistically significant association was observed between malformation type (high-flow vs. low-flow) and SF-36 score, but these data were statistically weak because of the small number of patients with high flow lesions (n=9).

In our cohort, one patient with lymphovenous malformation and overgrowth was diagnosed with Klippel-Trenaunay syndrome. Breugem et al.(16) found no association between leg length discrepancy and HRQoL, however, the number of patients with leg length discrepancy was small, and this parameter was evaluated subjectively by the patients, which may have introduced biases. In our patient cohort, overgrowth was evaluated clinically and not radiographically, and it is possible that discrete leg length discrepancies in some patients were overlooked. Further, patients with severe overgrowth are often referred for diagnostic

evaluation earlier in life and thus not be part of the population included in this study. We did not plan to include leg length discrepancy as a variable in our analyses, but association between overgrowth and HRQoL should be assessed in future studies and with accurate methods for leg measurements.

To the best of our knowledge, two previous studies of comparable design have been published. Breugem et al. (16) assessed quality of life in 82 patients with vascular malformations in the lower extremities. Compared to a Dutch reference population, the patients had lower mean SF-36 scores only for the *Vitality* and *Bodily pain* domains, no other significant differences were observed. However, the data was not age adjusted and thus the differences in mean SF-36 score between the groups may have been underestimated. We included patients with vascular malformations in any anatomical location outside the central nervous system, which may also have contributed to the different results. In contrast to our results, they found no association between muscle- or bone involvement and SF-36 scores, which could be explained by the different patient population and different variables in the regression model. Fahrni et al. (17) analyzed HRQoL with SF-36 in 71 patients with vascular malformations outside the central nervous system. In accordance with our study, they found significant lower physical- and mental summary scores in the patient cohort than in a German reference population, concluding that these patients have poorer quality of life. No differences were observed between sub-types of vascular malformations. In a recently published meta-analysis by Nguyen et al. (27) which included 6 studies and a total number of 320 patients with vascular malformations, higher bodily pain and worse mental health was reported, when SF-36 scores were compared with the United States general population.

Our data revealed significant differences in SF-36 scores in most of the domains; however it remains a fair question whether a statistically significant difference reflects a clinically relevant difference in HRQoL. It is reasonable to assume that the large differences found in

Bodily pain and *Role limitation due to physical problems* have clinical relevance. However, no clinical cut-off value regarding SF-36 scores exists, and it is debatable whether our findings represent a clinically relevant difference, rather than a statistically significant difference facilitated by the large reference population in our study. To assess the severity of HRQoL impairment, comparing our results with other populations of young chronically ill patients would be of interest. In a recent publication by Jansson et al., HRQoL was assessed in 181 patients with type-1 diabetes and a mean age of 33 years (28). Our patient population scored lower in the physical domains, with the most pronounced difference in *Bodily pain* (56.4 vs. 77) and *Role limitation due to physical problems* (58.1 vs. 77). Also, our population scored slightly lower in the mental domains, most significant in *role limitations due to emotional problems* (76.3 vs. 85), suggesting a more severe HRQoL impairment in our population than in a diabetic population, both physically and mentally. Assa et al. published SF-36 scores in 157 patients with anterior knee pain (previously known as patellofemoral syndrome) and a mean age of 30.3 years (29). Our population scored higher in all physical domains, most significant in *role limitations due to physical problems* (58.1 vs. 39.5). Also, we found higher scores in the mental domains, with the biggest difference in *limitation due to emotional problems* (76.3 vs. 64.8). Bodur et al. measured HRQoL in 962 patients with ankylosing spondylitis and a mean age of 39.4 years (30). Our population had higher SF-36 scores in all domains, except from *Vitality*. This indicates a more severe HRQoL impairment in patients with chronic musculoskeletal pain, than in our population of vascular malformation patients.

SF-36 is a non-disease specific tool suitable for HRQoL comparison between a population of patients and the general population, as in our study. Another way of performing HRQoL measurements would be to use a disease-specific tool, given that a normative score in such a tool is established and validated. One could argue that this would provide a more reliable measure, as typical clinical characteristics and symptoms associated with the disease will be taken into account. This also applies in studies evaluating treatment effect in patients with

chronic diseases, as radiology and laboratory tests have little relevance. Such a tool has not yet been established for vascular malformations, but according to a publication by Horbach et al. (31) a group of leading physicians is now in the process of developing a standardized tool for treatment outcome measures in patients with vascular malformations, the so-called Outcome measures for VAscular MAlformations (OVAMA) project. Another option for measuring treatment effect is the recently developed generic tool for treatment evaluation; the Patient-reported Outcome Measurement Informative System (PROMIS) (32).

There are several limitations in this study. Firstly, we did not have data on important demographic characteristics like level of education, income, lifestyle behavior and relationship status. We know that level of education is associated with SF-36 scores (20), and including such data in the analysis could have influenced the results. Secondly, despite having a sample of 111 patients, a larger sample would have provided more statistical power and more precision in our estimates. Finally, the data is based on assessment of a sample of patients who were referred to our clinic, most of them in order to be evaluated for treatment. Many patients with vascular malformations are asymptomatic, and it is not unlikely that the patients in our study had more complaints than the average vascular malformation patient.

In conclusion, our data revealed that patients with vascular malformations outside the central nervous system have lower SF-36 scores than the general Norwegian population, suggesting impaired HRQoL in this patient group. Higher age and muscle-/bone involvement were associated with lower SF-36 scores, mainly for the physical items. The results add knowledge that may be of value when considering treatment indications.

Conflict of Interest: None

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Table 1. Demographic, clinical and MRI characteristics of the patient cohort. Categorical data described as counts and percentages.		
Age (median, range)	27 years (14-63)	
	Categories	n (%)
Sex	Male	47 (42.3%)
	Female	64 (57.7%)
Diagnosis	Venous malformation	96 (86.5%)
	AV-malformation	9 (8.1%)
	Arteriolo/Capillary Venous malformation	4 (3.6%)
	Lymphatic malformation	1 (0.9%)
	Venolymphatic malformation (Klippel-Trenaunay syndrome)	1 (0.9%)
Anatomical location	Head and neck region	27 (24.3%)
	Upper extremity	22 (19.8%)
	Trunk	11 (9.9%)
	Lower extremity	51 (45.9%)
Tissue layer	Subcutis	35 (31.5%)
	Muscular	30 (27%)
	Subcutis and muscular	35 (31.5)
	Subcutis, muscular and bone	7 (6.3%)
	Bone	1 (0.9%)
	Subcutis, muscular and internal organs	1 (0.9%)
	MRI not performed	2 (1.8%)
Margins	Well defined	55 (49.5 %)
	Ill defined	41 (36.9 %)

	Both ill and well defined	13 (11.7%)
	MRI not performed	2 (1.8%)

Table 2. Univariate analysis showing mean SF-36 scores in a Norwegian reference population and in the patient cohort, mean difference (95% confidence interval) and p-value.

Domain	Reference population	Patient cohort	Mean Difference	p value
Physcial functioning	86.3	79.8	6.5 (2.8-10.3)	<0.01
Social functioning	87.2	79.3	7.9 (3.9-12.0)	<0.01
RLDT physical problems	75.5	58.1	17.4 (10.1-24.7)	<0.01
RLDT emotional problems	88.3	76.3	12.0 (6.7-17.5)	<0.01
Mental health	80.8	75.2	5.6 (2.0-9.2)	<0.01
Vitality	59.3	52.4	6.9 (3.1-10.7)	<0.01
Bodily pain	64.9	56.4	8.5 (4.1-13.0)	<0.01
General health	71.5	68.3	3.2 (-0.9-7.3)	0.174

RLDT=role limitation due to

Table 3. Multivariate analysis adjusted for age and gender. B coefficient with 95% confidence interval reflects difference in SF-36 score between the patient cohort and a normal Norwegian population.

Domain	B coefficient	95% CI
Physcial functioning	-17.22	(-20.99, -13.45)
Social functioning	-7.53	(-11.81, -3.24)
RLDT physical problems	-31.56	(-39.17, -23.96)
RLDT emotional problems	-13.7	(-19.46, -7.94)
Mental health	-1.79	(-4.75, 1.19)
Vitality	-2.42	(-6.45, 1.62)
Bodily pain	-13.57	(-18.25, -8.88)
General health	-6.35	(-10.78, -1.95)

RLDT=role limitation due to

Table 4. Multivariate analysis showing association between selected variables and SF-36 score in the patient cohort. B-coefficient (95% confidence interval).

	Pysical functioning	Social functioning	RLDT physical problems	RLDT emotional problems	Mental health	Vitality	Bodily pain	General health
Type	-8.50	3.75	-12.41	-3.54	-0.43 (-14.26,	10.69	-6.83 (-24.26,	-2.06
High flow vs. Low-flow	(-23.44, 6.44)	(-22.28,14.78)	(-42.02, 17.21)	(-31.00, 23.89)	13.39)	(-3.48, 24.85)	10.60)	(-19.12, 15.01)
Tissue layer								
muscular/bone vs.	8.52	2.59	**21.97**	2.17	1.89	5.32	**13.31**	1.03
subcutis	(-0.39, 17.42)	(-8.45, 13.63)	**(4.33, 39.61)***	(-14.17, 18.50)	(-6.36, 10.11)	(-3.12, 13.75)	**(2.93, 23.69)***	(-9.14, 11.20)
Margins								
ill-defined vs. well	-2.98	-1.95	-13.66	-3.44	-1.63	-5.12	-5.10	-4.03
defined	(-11.09, 5.14)	(12.01, 8.11)	(-29.74, 2.42)	(-18.33, 11.45)	(-9.14, 5.87)	(-12.81, 2.57)	(-14.53, 4.40)	(-13.30, 5.24)
Anatomical location								
Head and neck vs.	-6.05	3.67	-6.85	6.41	2.27	1.44	-9.35	-4.99
Trunk/extremities	(-16.25, 4.16)	(-8.99, 16.32)	(-27.08, 13.38)	(-12.32, 25.14)	(-7.17, 11.72)	(-8.23, 11.11)	(-21.25, 2.56)	(-16.65, 6.67)
Gender								
	-3.75	-3.74	5.25	-8.65	0.47	-1.69	-6.03	-7.55
Male vs. Female	(-11.89, 4.40)	(13.84, 6.37)	(-10.89, 21.40)	(-23.60, 6.30)	(-7.06, 8.01)	(-9.41, 6.03)	(-16.53, 3.48)	(-16.86, 1.75)
Age								
	-0.34	-0.36	-0.51	**-0.59**	-0.12	0.03	**-0.40**	**-0.43**
years	**(-0.65, -0.03)***	(-0.74, 0,03)	(-1.12, 0.11)	**(-1.16, -0.01)***	(-0.41, 0.17)	(-0.27, 0.33)	**(-0.76, -0.04)***	**(-0.79, -0.08)***

RLDT = Role limitation due to

*=significant association between variable and SF-36 score (5% significance level).