Quality of Life in Swiss Patients With Spongiform Venous Malformations

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Abstract. *Background/Aim:* Spongiform venous malformations (sVMs) get symptomatic in >90% of cases during a person's lifetime. Misdiagnosis is still common and treatment often incomplete, making this disease a lifelong issue for patients with a relevant impact on their quality of life. *Patients and Methods:* Medical records and imaging studies of patients with VMs from April 2002 to January 2017 were reviewed for confirmation of diagnosis and classification of the VMs. Only sVMs were included. Subjective data were obtained from the survey related to indication, response, and complications. We analyzed the frequency of correct diagnosis and Quality of Life by an SF12-based questionnaire for sVM-related issues in Swiss patients. *Results:* A total of 80 patients were included in the study. Forty-six (58%) patients were females. Patients were 11.6-77 years old with a median age of 28.1 years. The correct diagnosis according to the ISSVA-classification after having been seen at our Institution was 87%. Thirty-one (39%) patients responded to the survey. Sixteen (51%) were female. Twenty-eight (90%) patients felt that their sVM-related state of health improved within a year. Twelve (39%) patients reported that they could not work as good as normal because of slight to modest impairment by the sVM, while 19 (61%) patients were unimpaired. Mental impairment was found in 8 (26%) patients, while 23 (74%) patients felt no impairment. Eight (26%) patients reported that they were impaired within social contacts due to their sVM. Only 9 (29%) patients reported that venous malformation was

diagnosed around birth. Twenty-three (74%) patients received a wrong diagnosis. Patients that were treated, reported close to complete relief of symptoms in 26% (8 patients) while also 26% (8 patients) reported no change of symptoms after therapy. *Conclusion:* Swiss sVM patients also suffer from misdiagnosis and late diagnosis. They are impacted in their daily life by their disease.

Venous malformations (VMs) are dysmorphic venous channels that present in various ways (1). They can be relatively localized but also extensive within one or more anatomic regions. Venous malformations can be divided in 4 types: Spongiform, aneurysmal, reticular and phlebectatic (1). Spongiform venous malformations (sVMs) are the most often treated vascular malformations as these lesions get symptomatic in >90% during lifetime (2, 3). VMs have typical cellular characteristics, such as flat endothelium, dysplastic walls, and thin basement membranes (4). The head, limbs, or trunk are the main locations, but they are also found in the internal viscera, bones and in skeletal muscle (5). It is assumed that 100% of VMs are present at birth, and more mutations responsible for venous malformations become identified such as a gene that codes for an endothelial receptor on chromosome 9p (6). In general, single lesions are mostly due to a somatic mutation while multiple lesions are often caused by a hereditary genetic mutations (7). Superficial VMs are clinical apparent at birth, but are often misdiagnosed (8). While >90% of VMs progress during childhood and in younger adults, the cause of natural progression in older people is unknown and may be due to softening of the vein walls as in primary varicose veins. The primary indication for invasive treatment of VMs is pain, which mostly results from recurrent intralesional thrombosis. Treatment indication is also given when VM involve the airways, or those with articular involvement or disfigurement as well as gastro-intestinal bleeding (9-12). As

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Figure 1. Spongiform venous malformation. (A) Venous malformation with typical appearance. (B) Ultrasound image of spongiform venous malformation with recent thrombosis (arrow). (C) T2-fat-saturated image of spongiform venous malformation of deep back muscle (arrow).

VMs in general enlarge over time, treatment should be initiated early, as smaller lesions are easier to treat (8). Small, painless VMs of the extremities can be managed conservatively sometimes by wearing compression stocking while first-line treatment of symptomatic spongiform venous malformations (sVMs) is sclerotherapy with Aethoxysclerol (normally in a 3% concentration), dehydrated ethanol, sodium tetradecyl sulfate 3% (STS) and bleomycin being the most common sclerosants (13, 14) (Figure 1). The recurrence rate after incomplete removal is high and postoperative complications like damage to nerves are common, especially in case of surgical treatment (15).

Complete cure is possible, but treatment is often incomplete, making this disease a lifelong issue for patients with a relevant impact on their quality of life (16). Other studies assessed the outcome and complications of sclerotherapy for lymphatic malformations as well as for venous malformations performed have shown a decrease of symptoms after treatment (17-20). The SF Quality of Life Questionnaire (SF-12) questionnaire is frequently used to assess quality of life (QoL) after medical interventions (21-23). We conducted a retrospective analysis based on the SF 12 Quality of Life Questionnaire Version 2 (SF-12) of (un)-treated sVMs to assess quality with or without treatment as well as rates of misdiagnosis and other sVM-related issues in Swiss patients.

Patients and Methods

This study protocol was approved by the cantonal Ethics Committee and is in accordance with the guidelines of Helsinki. Medical records and imaging studies of patients with VMs from April 2002 through January 2017 were reviewed. Imaging studies were reviewed by specialists with experience in the diagnosis of vascular anomalies for confirmation of the diagnosis and classification of the VMs. Demographic and clinical data extracted from medical records and imaging studies included age, sex, anatomic location of the VM. Only sVMs were included. Subjective data was obtained from the survey related to indication, response, and complications. Patient's and/or their guardians/caregivers were sent a 21-item survey. The first part was based on the 12-SF questionnaire on quality of life,

while the second part was adopted to a questionnaire previously used in assessment of VMs.

Inclusion criteria: Patients with sVMs. Exclusion criteria: Patients with VMs that are not of the spongiform type or other vascular malformations. Anatomical regions of VM location and treatment were categorized as: 1. Head/neck. 2. Upper extremities. 3. Lower extremities. 4. Torso. 5. Multiple.

Data was extracted from medical records included demographics, and medical history. Specifically, anatomic location of VMs, correctness of diagnosis when referred and after clinical visit, and treatment were noted. Imaging studies included CT-scans, MRIs, and ultrasound imaging.

Surveys were sent to 80 patients. If they did not respond they were sent a second survey. If they did not respond to the second survey, they were contacted *via* phone or email and if the patient agreed, a third questionnaire was sent. Of these 80 patients, 31 patients (39%) responded to the survey. These 31 patients were included in the survey analysis.

The survey consisted of two parts: A) SF 12 health related to venous malformation, B) Venous malformation related. The survey questionnaire included 21 items either on a subjective one-to-three, or a one-to-five-grade scale.

Quality control (Q/C) was assured through back-checking of entered data against the original questionnaires. The entries were double checked by a second investigator. Frequency distributions were double checked. Incomplete, incorrect, inaccurate, and irrelevant data was removed from the final database to ensure accuracy and completeness.

Results

We included 80 patients with sVMs into this retrospective cohort study and analyzed their data. Forty-six (58%) patients were female. Patients were 11.6-77 years old with a median age of 28.1 years. The correct diagnosis based on external or internal imaging as well as clinical visits when seen at our institution according to the ISSVA-classification was 88.8%. All lesions were identified as vascular anomalies. Baseline characteristics are presented in Table I. Seventy patients received interventions. These patients were 11.6-71 years old at intervention with a median age of 31.5 years.

The survey results are presented in Table II. Not all patients' answers are displayed in detail to keep a clear view

Table I. *Baseline characteristics of included patients.*

Baseline characteristics	
All patients	
Number of patients	80
Gender female/male	46/34
Age in years	11.6-71.0
Median age in years	28.1
Median age at intervention in years	31.5
Correct diagnosis	71 (88.8%)
No. of patients that responded to survey	31
Gender female/male	16/15
Age	12.3-71.0
Median age	29.6
Correct diagnostics	27 (87%)
Area treated (total number of treatments in %)	
Head/neck	1 (1)
Torso	1 (1)
Lower extremities	14 (26)
Upper extremities	9 (22)
Multiple locations	1 (5)

on the focus of this paper. Thirty-one (39%) patients responded and sent back the survey. Sixteen (51%) of the responding patients were female. Responding patients were 12.3-71 years old with a median age of 29.6 years. Of the patients that responded to the survey, 26 had received treatment. Treated areas were head/neck 1 (4%), torso 1 (4%), upper extremities 9(35%), lower extremities 14 (54%) and multiple locations in 1 (4%) case.

The first part of the survey was based on the SF12 questionnaire for Quality-of-Life version 2 and referred to the influence of the sVMs on the QoL. Two questions compared the actual state of health to the state of health related to the venous malformation a year ago. Twenty-eight (90%) patients felt that their sVM-related state of health was better (either excellent, very good or good), while only 3 (10%) patients reported a worse state of health ("less good" or "bad").

One question focused on how physical abilities in daily life (such as heavy work, walking, carrying bags, and 6 other items) were impaired by the sVM. Only 3 (10%) patients reported that they were strongly impaired by the sVM, while 11 (30%) patients were slightly impaired, and 18 (58%) patients were not impaired when performing strenuous activity. If walking more than 1,000 meters, 6 (20%) patients felt impaired, while 25 (80%) did not. Twelve (39%) patients reported that they couldn't work as good as normal because of slight to modest impairment by the sVM during the last 4 weeks, while 19(61%) patients were unimpaired. Being asked if they were mentally impaired (being sad, feeling bad, *etc.*) by the malformation, 8 (26%) patients reported some impairment, while 23 (74%) patients felt no impairment.

Three more questions focused on this subject bearing the same response and outcome. Correlating to this, 8 (26%) patients reported that they were impaired within social contacts during the last 4 weeks.

The last question focusing on the QoL focused on whether the patients felt a tendency of being sick (not only related to the VM but the general health) compared to their peer group. Only few 3 (10%) patients felt that they were sicker or had a higher tendency towards other diseases than their peer group.

The second part of the survey was directly related to VM. Only 9 (29%) patients reported that VM was diagnosed around birth. The other patients received diagnosis during their lifetime. Twenty-three (74%) patients received a wrong diagnosis before the VM was diagnosed correctly. This means that only 26% (8) patients were diagnosed correctly when having been examined for their VM for the first time. Common misdiagnosis was "hemangioma", "tumor", or "cystic hygroma" amongst others. Twenty-six (84%) patients reported increase of the symptoms during their lifetime, with a slow progression within in the last 5 years and 22 (71%) patients an even slower progression before that. Nine (30%) patients reported an increase of the lesion due to a defined event, such as pregnancy.

Being asked about symptoms, most patients complained about pain 29 (94%) and swelling 27 (87%). Previous infections were mentioned by 2 (6%) patients. Five (16%) patients felt very disturbed by their physical appearance due to the malformation, while 16 (52%) patients reported minor disturbance due to their physical appearance related to the sVM. Ten (32%) patients were very worried about possible complications due to the sVM and 10 (32%) patients less concerned. Eleven (35%) patients were not concerned about complications. Patients were asked how often the sVM was symptomatic: Nine (30%) patients reported that the sVM was symptomatic every day; six (19%) patients reported symptoms on a weekly base; eight (26%) patients reported monthly symptoms, and 5 (16%) patients reported yearly symptoms. Twenty-six (84%) patients reported active treatment of the sVM. Sixteen (52%) patients received sclerotherapy, 4 (13%) patients reported additional endovenous laser ablation. Surgical procedures were performed in 12 (39%) cases. Additional compression therapy in extremity sVMs was performed in 8 (26%) patients and 8 (26%) patients received painkillers for treatment of symptomatic lesions.

Eight (26%) patients that had received active treatment (such as sclerotherapy) reported a relevant relief of symptoms, while also 26% (8 patients) reported no change of symptoms after such therapy. Seven (23%) patients reported a long-lasting relief of symptoms while 3 (10%) patients reported relief for some time after treatment but no permanent relief. Nine (29%) patients reported complications after any therapy, such as relevant pain and swelling after

Table II. Survey results.

Question	Excellent		Very good		Good		Less good		Bad					
How would you describe your state of health in general?	5	16%	10	32%	13	42%	1	3%	2	6%				
Question	Much better than a year ago		Somewhat better than a year ago		About the same as a year ago		Somewhat worse than a year ago		Much worse than a year ago					
Compared to last year, how would you rate your current state of health?	2	6%	4	13%	21	68%	3	10%	1	3%				
Question					Yes, strong limitations		Yes, somewhat limited		No, not restricted at all					
Does your current health condition make you unable to perform these activities?														
3.1 Strenuous activity <i>e.g.</i> , fast running, sports					2	6%	11	35%	18	58%				
3.2 Medium activity <i>e.g.</i> , Vacuum cleaning, moving the table, playing golf					0	0%	7	23%	24	77%				
3.3 Lift or carry shopping bags					3	10%	4	13%	24	77%				
3.4 Climb several stairs					0	0%	3	10%	28	90%				
3.5 Climb a single stair					0	0%	1	3%	30	97%				
3.6 Bend, bend your knee					1	3%	5	16%	25	81%				
3.7 Walk more than 1 km					2	6%	4	13%	25	81%				
3.8 Walk several hundred meters					0	0%	2	6%	29	94%				
3.9 Walk one hundred meters					0	0%	2	6%	29	94%				
3.10 Bathing or dressing					0	0%	1	3%	29	94%				
Total average					1	3%	4	13%	26	84%				
Question					Always		Mostly		Sometimes		Rare		Never	
Last 4 weeks, how many times did you visit the hospital due to your physical difficulties at work or at home?														
4.1 I could not work as usual	1	3%	1	3%	6	19%	4	13%	19	61%				
4.2 I have achieved less than I wanted	0	0%	2	6%	5	16%	5	16%	19	61%				
4.3 I could only do certain things	1	3%	3	10%	5	16%	3	10%	19	61%				
4.4 I had difficulties with the execution	1	3%	3	10%	5	16%	4	13%	18	58%				
Total average	0	2%	2	7%	17	54%	4	13%	19	60%				
Question					Always		Mostly		Sometimes		Rare		Never	
Last 4 weeks, how many times have you felt down or anxious due to mental issues or any other difficulties at work or at home?														
5.1 I could not work as usual	1	3%	1	3%	3	10%	7	23%	19	61%				
5.2 I got less done than I wanted	1	3%	2	6%	5	16%	5	16%	18	58%				
5.3 I could not work as careful as I used to work	1	3%	1	3%	3	10%	5	16%	21	68%				
Total average	1	3%	2	6%	6	20%	5	15%	19	61%				
Question	Not at all		Somewhat		Moderate		Quite		Very					
How much did your physical or mental health problems affect your daily contact with your family, friends, neighbors, or acquaintances in the last four weeks?	23	74%	4	13%	1	3%	3	10%	0	0%				

Table II. Continued

Table II. *Continued*

Question										
How often in the past 4 weeks have you been	Always		Mostly		Sometimes		Rare		Never	
Full of life?	11	35%	10	32%	8	26%	1	3%	0	0%
Very nervous?	0	0%	3	10%	6	19%	13	42%	9	29%
So down that nothing could cheer you up?	0	0%	1	3%	5	16%	9	29%	16	52%
Calm and exuberant?	4	13%	17	55%	3	10%	6	19%	0	0%
Full of energy?	5	16%	15	48%	7	23%	3	10%	1	3%
Discouraged and sad?	0	0%	3	10%	5	16%	9	29%	14	45%
Exhausted?	1	3%	0	0%	12	39%	12	39%	5	16%
Happy?	9	29%	16	52%	5	16%	0	0%	1	3%
Tired?	2	6%	6	19%	15	48%	6	19%	2	6%
Total average	4	11%	8	25%	7	24%	7	21%	5	17%

Question										
To what extent does each of the following statements apply to you?	True entirely		Largely applicable		Don't know		Does not apply to a large extent		Does not apply at all	
I seem to get sick more easily than others	1	3%	5	16%	6	19%	7	23%	12	39%
I am as healthy as other people I know	11	35%	11	35%	3	10%	4	13%	2	6%
I expect my health condition to deteriorate	1	3%	2	6%	7	23%	11	35%	10	32%
My health is excellent	8	26%	12	39%	2	6%	5	16%	4	13%
Total Average	5	15%	7	24%	7	23%	6	21%	5	17%

Question										
							By birth		Later	
When were you first diagnosed with venous malformation?							9	29%	23	74%

Question										
							Wrong diagnosis		Correct diagnosis	
Was the venous malformation named otherwise (<i>e.g.</i> , as a hemangioma)?							23	79%	9	29%

Question										
			Yes		No		Stable		Become less	
Has the venous malformation increased during your lifetime?			26	81%	3	9%	2	6%	0	0%
Have the complaints caused by the venous malformation increased over the years?			14	44%	10	31%	5	16%	3	9%

Question										
How much is your life quality limited due to the venous malformation complaints?	Strong		Medium		Low		Not at all		Cannot say	
A. Pain	4	13%	10	32%	15	48%	2	6%	0	0%
B. Swelling	3	9%	10	31%	14	44%	5	16%	0	0%
C. Infections	0	0%	0	0%	2	6%	24	75%	6	19%
D. Appearance	5	16%	6	19%	10	31%	11	34%	0	0%
E. Concerned about complications	5	16%	5	16%	10	31%	12	38%	0	0%
F. Others	2	13%	4	27%	0	0%	9	60%	0	0%
Total average	3	11%	6	20%	9	29%	11	36%	1	3%

Table II. *Continued*

Table II. Continued

Question	Yes		No	
A. Have you carried out a treatment for venous malformation?	26	81%	4	13%
A1 Sclerotherapy/Embolization	63	80%	16	20%
A2 Laser treatment	75	95%	4	5%
A3 Compression therapy	71	90%	8	10%
A4 Operation	67	85%	12	15%
A5 Blood thinning (LMWH, vKA, ASS)	70	89%	9	11%
A6 Painkiller	70	90%	8	10%
B. Overall, have the treatment(s) improved/reduced the symptoms?	8	30%	8	30%
C. Are there any adverse events or adverse reactions during treatment?	9	36%	14	56%
C1 Pain	73	92%	6	8%
C2 Swelling	72	91%	7	9%
C3 Thrombosis or phlebitis	79	100%	0	0%
C4 Nerve damage	74	94%	5	6%
C5 Wounds on the treated area	76	96%	3	4%
C6 Other	74	94%	5	6%

ASS: Acetyl-salicyl-acid; LMWH: low molecular weight heparin; vKA: Vitamin K-antagonist.

sclerotherapy. Nerval injury after surgery was reported in 5 (16%) patients. Ulceration after treatment appeared in 3 (10%) patients. Deep venous vein thrombosis was not reported as complication.

Discussion

Misdiagnosis of patients with vascular malformations is still common. In this cohort, only the minority of patients received the correct diagnosis when examined for the first time. Correct diagnosis according to the ISSVA-classification was established after being seen at a University Hospital. Common misdiagnosis in this cohort was “hemangioma”, “tumor”, or “cystic hygroma” amongst others. These findings are consistent with above mentioned studies and reflect the problem of other rare diseases: a correct diagnosis is challenging and often results in a long odyssey for the patient (8, 24). Vascular malformations are often given different names depending on the classification used or on the clinical speciality that gives the diagnosis (24). It is not unusual that the same lesion is given multiple names within one scientific publication (25). Plenty of published articles, mostly case reports, give wrong diagnosis or mix up unrelated vascular anomalies, such as the “Klippel-Trénaunay-Parkes-Weber-Syndrome”(26). When searching the National Library of Medicine >30 matches are found for “Klippel-Trénaunay-Parkes-Weber-Syndrome” when mentioned in the title, including Journals with a high Impact Factors. While KTS is a combined slow-flow lesion, PWS is a high-flow lesion with a different underlying genetic mutation (26, 27). There is an ongoing discussion on the topic of misnomers and correct diagnosis in vascular

malformations (28, 29). Without vilifying the achievements of former and current researchers that have given particular names to circumscribed and defined vascular anomalies, the authors think in accordance with ISSVA that correct diagnosis of vascular malformations would benefit from the description of the involved vessel types (*e.g.*, venous and lymphatic), adding information on under- and overgrowth and if possible, on the genetic underlying cause, and other important clinical findings, knowing, that wrong diagnosis causes wrong treatment in vascular anomalies (*e.g.*, betablocker treatment in venous malformations) (30).

Pain and swelling, the main two complaints in patients within sVM, have a relevant impact on QoL and are the principal treatment indication. Data on QoL is available for different forms of venous diseases, such as DVT or pelvic congestion syndrome (31, 32). The negative impact of varicose veins on QoL and the positive effect after successful treatment is long known (33, 34). Evaluation of QoL after treatment of vascular malformations evaluated by surveys was performed earlier in relatively small cohorts. Berger *et al.* assessed Health-Related Quality of Life in a population of patients with VMs and compared the results with data from a national reference population in Norway (35). Their data also suggests that patients with vascular malformations impair QoL. They did compare cohort with the general population using the Short-Form 36-item questionnaire which also covers both physical and mental aspects and is the more extended form of the SF-12. We could confirm this finding in Swiss patients, that current health status was in 90% positive but 40% of patients reported impairment due to the sVM. A quarter of patients reported mental impairment due to the sVM. 26% patients reported that they were

impaired within social contacts. QoL was also examined in conservatively managed patients as well as in active treated patients. Treatment of sVMs included invasive treatment (with sclerotherapy being the first-line treatment) and/or conservative treatment. Yun *et al.* found in their cohort of 207 patients who had been managed conservatively that based on responses to their questionnaire, the size and symptoms of VM progressed in 32% of patients over the course of their life (36). They could identify VMs combined with CM or LM as independent predictor of progression. The percentage of patients that had increasing symptoms due to the sVM was higher (86%) in our cohort, which is in accordance with other published studies that showed progression of symptoms in >90%(2). This high percentage of progression is also found in arteriovenous malformations and in lymphatic malformations (37, 38).

Rautio *et al.* included 23 patients that had completed treatment with ethanol sclerotherapy in their study and evaluated the quality of life after treatment, as well exploring psychological, physical, social functioning, and pain (39). Sixteen patients were symptomless after a year or more and the results concerning QoL showed that most patients did well after endovascular treatment. An overall degree of satisfaction with the treatment of craniofacial venous malformations in children and adults of 78% patients was reported by Berenguer *et al.* (40). Van der Linden *et al.* could also show that patient satisfaction was correlated to long-term outcome in VMs after treatment (41, 42). Their group achieved a sustainable improvement for half of the patients during a 5-year follow-up period. The above findings are in generally consistent with another study from 2017 that sclerotherapy for treatment of venous malformations results in significant reduction of symptoms. Despite multiple treatments needed patients were willing to undergo these (20). The recurrence rate after incomplete removal is high and postoperative complications like damage to nerves are common, especially in surgery (15). We could also confirm this in our cohort as nerve injury was the most frequent complication after surgery.

Conclusion

Although living in a country with one of the most advanced health care systems in the world, patients with vascular malformations still suffer from misdiagnosis, late diagnosis and incomplete treatment. They are impacted in their daily life by their disease. This leads us to the conclusion that in the adult medical community there still is a lack of awareness for vascular anomalies and that diagnosis and treatment should preferably be performed in specialized centers with a fix group of health personal working together. This group would be preferably from different specialties but should use the same nomenclature.

Conflicts of Interest

R.C. reports having received the “Förderungspreis USGG Switzerland” for this project. There are no other conflicts of interest.

Authors' Contributions

B.S. contributed to the data, performed the analysis, wrote the manuscript, and reviewed the paper. D.H. analyzed the data, wrote the paper, and reviewed the paper. M.K. contributed to the data and reviewed the paper. T.M. collected data, contributed to the data, and reviewed the paper. S.E. reviewed the results, contributed to the style, and reviewed the paper. R.C. designed the study, collected data, contributed to the data, wrote the paper, and reviewed the paper.

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