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Original Article

Study on new classification and treatment of vascular malformations in the extremities

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Abstract: Objective: To propose a new clinical classification of vascular malformations (VMs) in the extremities, and to investigate the correlation between the new classification and the effectiveness of treatment. Methods: We retrospectively analyzed the clinical data of 256 patients who were treated in our hospital for VMs in the extremities, including their clinical characteristics, imaging data, conventional classification, treatment process and prognosis. Based on the extent of lesion determined by the imaging test, the cases were classified into six categories, which were superficial type, mono-localized type, poly-localized type, extensive type, nerve type, and diffuse type. The treatment process and treatment outcome in all the patients were analyzed, and the correlation between the new classification and the treatment effectiveness were investigated. Results: According to the conventional classification, the lesions (256 cases) could be divided into high-flow VM (arteriovenous malformation, 77 cases) and low-flow VM (venous malformation, 179 cases), while according to the new classification, they could be classified into six types, which were superficial type (84 cases), mono-localized type (56 cases), poly-localized type (23 cases), extensive type (74 cases), nerve type (9 cases), and diffuse type (10 cases). Treatment methods were as follows: most of the patients with superficial type received laser treatment (80/84); most of the patients with mono-localized type or poly localized type underwent surgical excision only (25/56, 12/23); among patients with extensive type, 21 of them underwent surgical excision only (21/74), while 34 received surgical excision plus muscle transfer (34/74); patients with nerve type underwent surgical excision only (2/9) and embolization of draining vein and sclerotherapy (7/9); more than half of the patients with diffuse type received embolization of draining vein and sclerotherapy (6/10, the other 4 patients didn't received any treatment). Patients were followed up for 1-10 years (average 6.5 years). Under the conventional classification based on the hemodynamics, the improvement rates in patients with high-flow type and low-flow rate were 84.42% and 94.97% respectively, whereas under the new classification based on the extent of lesion, the improvement rates in groups of superficial type, mono-localized type, poly-localized type, extensive type, nerve type and diffuse type were 95.24%, 98.21%, 95.65%, 87.84%, 55.56% and 80.00% respectively ($P<0.001$). Logistic regression analysis found significant difference in the prognosis between these two classifications ($P=0.02$). Conclusion: The new classification proposed in this study was found to be closely related to the prognosis of VMs in extremities, and treatments received by patients within the same group under the new classification tended to be the same. This finding suggests that the new classification can be applied clinically for assisting in the clinical diagnosis and treatment.

Keywords: Extremities, vascular malformations, therapeutics

Introduction

Vascular malformation (VM) is a common benign vascular lesion in soft tissues of extremities, which accounts for about 7% of the benign soft tissue tumors. It is mainly an abnormality in blood vessel structure, with no abnormal cell [1]. VMs in extremities are often manifested as extensive lesions, which can bring about severe complications, and even threaten the lives of patients [2, 3]. Surgery alone is likely to cause massive bleeding, and oftentimes cannot cure the disease completely. Meanwhile, VMs can extend to the joints and bones to cause severe complications, massive bleeding, handicap and even death, which create difficulties for the treatment [4]. In the past, VMs are often divided into two categories, which are high-flow type and low-flow type [5]. However, this type of classification is not closely related to patient's

prognosis, and provides very limited assistance in making treatment plans [6]. Due to the development of imaging and interventional technologies, new classifications are expected to be established. Therefore, based on patients' case histories and imaging results, the present study proposed a new type of classification, and investigated its correlation with the prognosis of the disease.

Materials and methods

Case selection

The clinical data of 256 cases of VMs (with complete medical records) were collected for the study. The study was approved by the Ethics Committee of People's Hospital of Linyi Economic and Technological Development Zone and informed consents were obtained from patients.

Inclusion criteria were as follows: patient met the diagnostic criteria of VM (test of X-ray and CT found phleboliths in soft tissues of extremities; vascular anomaly in extremities was detected by color ultrasound; abnormality in feeding artery was identified by DSA); patient aged between 18 and 70 years (with no restriction on gender); the treatment process was complete and patient was not lost to follow-up (follow-up period was 2 years).

Exclusion criteria: patients were found to have open blood vessel injuries of the extremities; patient had evident heart, liver, lung, or kidney failure.

Data extraction

The following information was collected for the study, which included patients' basic information (age, gender, underlying diseases), symptoms and physical signs, clear diagnosis, conventional classification, imaging results (DX, CT, MRI, ultrasound), pathological feature, complete treatment process with no missing information, follow-up period, and prognosis.

Information regarding the treatment methods was collected, which included parameters of laser treatment (such as laser type and power), and data related to the surgical excision (such as signs, excision area, whether or not there was any muscle transfer, embolization, and sclerotherapy). Based on these information, the treatment methods in patients were classified into five groups: 1) Laser treatment; 2) Surgical excision; 3) Surgical excision + muscle transfer; 4) Embolization of feeding artery + excision of tumor; 5) Embolization of draining vein + sclerotherapy.

The effectiveness of treatment was defined by using following criteria: 1) Cured: VM or vascular tumor was removed completely; patient could get back to normal life and experienced no recurrence during a more than one-year follow-up; 2) Markedly improved: the lesions were almost completely removed, or the tumor size was reduced by over 80%; the tumor was stable or grew slowly during follow-up period; patient had no sign of pain; the affected limb could function properly; 3) Improved: the main tumor in the lesion was removed, or the tumor size was reduced by over 30%; the pain was relieved and the function of the limb improved, which wouldn't keep patient from living normal life; 4) Not improved: the tumor was not noticeably reduced; patient's symptoms were not evidently improved and patient still couldn't get back to normal life [7].

Basis of the new classification

Lesions were classified into the following six types based on their extents: 1) Superficial type: the lesion was only in the superficial tissue, and didn't extend to the muscle; 2) Mono-localized type: the lesion was only in one area or one muscle; 3) Poly-localized type: the lesions were in the single muscle group of multiple areas, where less than 50% of the muscles were affected; 4) Extensive type: the lesions were in multiple areas or multiple muscle groups, where more than 50% of the muscles were affected; 5) Nerve type: the tunica vaginalis and perineurium of the nerve trunk in extremities were affected; 6) Diffuse type: the lesions existed in multiple muscle groups and soft tissues of the entire limb.

Outcome measures

The outcome measures were mainly about the differences in the prognosis between two classifications, which included the difference in the lesion progression, and whether or not there was any association between the new classification and the prognosis.

Table 1. Symptoms and physical signs

Symptoms	Case	Percentage (%)
Limb hypertrophy or presence of localized soft tissue masses	243	94.92
Blue skin	111	43.36
Red spots on skin	24	9.38
Increase in skin temperature	21	8.20
Pain in affected limbs	138	53.91
Affected limbs had different levels of deformities and malfunctions	38	14.84
Tumors were complicated by localized ulcers which later ruptured	6	2.34

Table 2. Treatment of patients under conventional classification

Treatment method	Case	High-flow type		Low-flow type	
		Case	%	Case	%
Laser treatment	94	42	54.55	52	29.05
Surgical excision	64	12	15.58	52	29.05
Surgical excision + muscle transfer	34	4	5.19	30	16.76
Embolization of feeding artery + resection of tumor	34	14	18.18	20	11.17
Embolization of draining vein + sclerotherapy	21	-	-	21	11.73
Amputation	5	3	3.90	2	1.12
No treatment	4	2	2.60	2	1.12
Total	256	77	100.00	179	100.00

Statistical analysis

SPSS software was applied for the statistical analysis. The count data were expressed as percentage (rate) and the measurement data were expressed as mean ± sd; comparison of the treatment effectiveness among individuals in different classification were performed by X^2 test.

The association between the method of new and conventional classification and the prognosis was analyzed by multiple logistic regression. The prognoses were divided to two groups, which were group of improvement and group of non-improvement. The method of binary classification was adopted. The conventional classification was taken as variable 1, and the high-flow and low-flow type were coded 0 and 1 respectively. The new classification was taken as variable 2, and the dummy variables were used in coding: the superficial type was taken as control X1=0, X2=0, X3=0, X4=0, X5=0; mono-localized type: X1=1, X2=0, X3=0, X4=0, X5=0; poly-localized type: X1=0, X2=1, X3=0, X4=0, X5=0; extensive type: X1=0, X2=0, X3=1, X4=0, X5=0; nerve type, X1=0, X2=0, X3=0, X4=1, X5=0; diffuse type: X1=0, X2=0, X3=0, X4=0, X5=1. Method of binary classification was used in gender and treatment effectiveness, in which the male and female were coded 0 and 1 respectively, and the improvement and non-improvement were coded 0 and 1 respectively. Gender, age, and type of classification were entered into the regression analysis (Backward: Wald). The alpha-to-enter significance level was 0.10, while the alpha-to-remove significance level was 0.15. A value of $P<0.05$ was considered as statistically significant.

Results

Basic information

Among the 256 patients from our hospital, there were 134 male patients and 122 female patients (the ratio of males to females was 1:1). The age distribution of the patients was as follows: 11 patients aged 18-20 years, 18 patients aged 21-25 years, 28 patients aged 26-30 years, 113 patients aged 31-40 years, 49 patients aged 41-50 years, 22 patients aged 51-60 years, 9 patients aged 61-70 years, and 6 patients aged over 70 years (mean age ± sd, 48.3±4.7). The average medical history was 8.9 years.

Table 3. Treatment of patients under new classification

Treatment method	Case	Superficial type		Mono-localized type		Poly-localized type		Extensive type		Nerve type		Diffuse type	
		Case	%	Case	%	Case	%	Case	%	Case	%	Case	%
Laser treatment	94	80	95.24	14	25.00	-	-	-	-	-	-	-	-
Surgical excision	64	4	4.76	25	44.64	12	52.17	21	28.38	2	22.22	-	-
Surgical excision + muscle transfer	34	-	-	-	-	-	-	34	45.94	-	-	-	-
Embolization of feeding artery + resection of tumor	34	-	-	17	30.36	6	26.09	11	14.86	-	-	-	-
Embolization of draining vein + sclerotherapy	21	-	-	-	-	-	-	8	10.82	7	77.78	6	60.00
Amputation	5	-	-	-	-	5	21.74	-	-	-	-	-	-
No treatment	4	-	-	-	-	-	-	-	-	-	-	4	40.00
Total	256	84	100.00	56	100.00	23	100.00	74	100.00	9	100.00	10	100.00

Table 4. Follow up of patients under conventional classification

	High-flow type	Low-flow type
Follow-up	77	179
Healed	36	70
Markedly improved	25	59
Improved	4	41
Not improved	12	9
Improvement rate	84.42	94.97
X^2 value	7.968	
P value	0.005	

Symptoms and physical signs

There were 243 cases (94.92%) in which patients' affected limbs were hypertrophic or presented with localized soft tissue masses (the diameter of the largest mass was about 3-4 cm), 111 cases (43.36%) where skin color turned blue, 24 cases (9.38%) where there were red spots on skin, 21 cases (8.20%) where skin temperature increased, 138 cases (53.91%) where pain existed in affected limbs (among which 18 cases reported unbearable pain (7.03%), and one patient suffered from secondary gastrointestinal bleeding due to long-term use of painkillers), 38 (14.84%) cases where the affected limbs had different levels of deformities and malfunctions, 6 (2.34%) cases where the tumors were complicated by localized ulcers which later ruptured and bled (2 cases were arteriovenous malformation (AVM) where blood spurted; 1 case was complicated by fingertip ischemia; 1 case was extensive AVM complicated by reduction in platelet count ($30*10^9$/L)). See **Table 1**.

Treatment plans

According to the conventional classification based on the hemodynamics, there were 77 patients with high-flow type, among which 42 received laser treatment, 12 underwent surgical excision, 4 received surgical excision plus muscle transfer, 14 received embolization of feeding artery and tumor resection, 3 underwent amputation, and 2 didn't receive any treatment. There were 179 patients with low-flow type, among which 52 received laser treatment, 52 received surgical excision, 30 received surgical resection and muscle transfer, 20 received embolization of feeding artery and tumor resection, 21 received embolization of draining vein and sclerotherapy, 2 received amputation, and 2 had no treatment. See **Table 2**.

Under the new classification based on the extent of lesion, cases were divided into six types, which were superficial type (84), mono-localized type (56), poly-localized type (23), extensive type (74), nerve type (9), and diffuse type (10). Among the patients with superficial type, 80 received laser treatment and 4 received surgical resection; for patients with mono-localized type, 14 received laser treatment, 25 received surgical resection only, and 17 received embolization of feeding artery and tumor resection; among patients with poly-localized type, 12 received surgical resection only, 6 received embolization of feeding artery and tumor resection, 5 underwent amputation; among patients with extensive type, 21 received surgical resection only, 34 received surgical resection and muscle transfer, 11 received embolization of feeding artery and tumor resection, 8 received embolization of draining vein and sclerotherapy; 2 patients with nerve type received surgical excision only, while another 7 patients with this type received embolization of draining vein and sclerotherapy; 6 patients with diffuse type received embolization of draining vein and sclerotherapy, and another 4 with this type received no treatment (**Table 3**).

Treatment effectiveness

Patients were followed up for 1-10 years (average 6.5 years). Under the conventional classification system, the improvement rates in patients with high-flow type and low-flow rate were 84.42% (65/77) and 94.97% (170/179) respectively. The improvement rates in both groups were compared by X^2 test, which returned the value 7.773, and found there was a significant difference (P=0.005). Under the new classification system, the improvement rates in the following six types were: 95.24% (superficial type), 98.21% (mono-localized type), 95.65% (poly-localized type), 87.84% (extensive type), 55.56% (nerve type), and 80.00% (diffuse type) respectively. The comparison of these improvement rates among the 6 types was conducted by X^2 test, which returned value 23.920, and showed that the

Table 5. Follow up of patients under new classification

	Superficial type	Mono-localized type	Poly-localized type	Extensive type	Nerve type	Diffuse type
Follow-up	84	56	23	74	9	10
Healed	62	44	-	-	-	-
Markedly improved	10	4	14	47	5	4
Improved	8	7	8	18	-	4
Not improved	4	1	1	9	4	2
Improvement rate	95.24%	98.21%	95.65%	87.84%	55.56%	80.00%
X^2 value			23.920			
P value			<0.001			

Table 6. Gender and effectiveness of treatment under two classifications

Gender	Classification	Treatment effectiveness	
		Improved	Not improved
Male	New classification	131	3
	Conventional classification	124	8
Female	New classification	119	3
	Conventional classification	117	5

differences had statistical significance (P< 0.001, **Tables 4** and **5**).

Correlation between treatment effectiveness and classification

The logistic regression analysis was performed to investigate the association between the two classifications and the improvement rates in patients with VMs in extremities. The result showed significant difference in the prognosis between two classifications (P=0.02), while gender had no impact on the prognosis (P=0.175). See **Tables 6** and **7**.

The result of the logistic regression analysis found that there was no significant difference in the improvement rates between high-flow type and low-flow type under conventional classification after treatment (P=0.05, OR=1.2), whereas there was great difference in improvement rates among various types under new classification. The improvement rates in mono-localized, poly-localized, and extensive type after treatment were similar to that in superficial type (P=0.236, P=0.998, P=0.144). As compared to control group, patients with nerve and diffuse type experienced evident improvement following treatment (P<0.001, OR=1.23; P=0.007, OR=2.43).

Discussion

Disease occurrence

VM in the extremities is mostly likely to occur in teenagers with no gender preference. In the present study, the average age of onset was 48.3±4.7 years, and most of the patients had the onset when they were aged between 31 and 40 years old (44.14%). Histories of these diseases lasted for 8.9 years on average. The ratio of males to females was 1:1. These data were consistent with other studies [8, 9].

Classification and treatment plan

Currently, the treatment plan was usually made based on the impact of the lesion on patient's quality of life. In most cases, the conservative treatment was applied. However, in the cases where patients experienced clinical complications, percutaneous puncture or interventional treatment would then be necessary. According to lesion's location, severity and level of deformity, sclerosants and embolic agents used in artery may need to be used in combination, such as ethanol, bleomycin, 3% sodium tetradecyl sulfate (STS), polidocanol and various coils and polymer microspheres [10, 11]. Ethanol sclerotherapy has been successfully applied clinically in some cases of low-flow VMs. It can be used as either a single treatment or a treatment before the operation [12, 13]. When treating high-flow VM, the aim of the treatment is to cut off arteriovenous fistula by ethanol. However, the sclerotherapy cannot solve this issue well, which may be partly due to the fact that ethanol can make the infused or injected drug flow out rapidly. So far,

Table 7. Impacts of the two classifications and gender on treatment effectiveness

		B	S.E	Wals	df	Sig.	Exp (B)
Step 1[a]	Variable 1			8.235	5	0.144	
	Variable 1 (1)	-0.482	0.407	1.404	1	0.236	0.617
	Variable 1 (2)	-18.786	7,882.490	0.000	1	0.998	0.000
	Variable 1 (3)	-1.124	0.770	2.132	1	0.144	0.325
	Variable 1 (4)	23.620	28,420.722	0.000	1	0.999	1.812E10
	Variable 1 (5)	1.319	0.723	3.329	1	0.068	3.738
	Constant	-2.417	0.279	75.102	1	0.000	0.089
Step 2[b]	Variable 1			13.437	5	0.020	
	Variable 1 (1)	-1.129	0.420	7.217	1	0.007	0.323
	Variable 1 (2)	-0.303	8,540.342	0.000	1	1.000	0.739
	Variable 1 (3)	17.359	3,286.914	0.000	1	0.996	3.460E7
	Variable 1 (4)	42.103	28,610.160	0.000	1	0.999	1.928E18
	Variable 1 (5)	19.802	3,286.914	0.000	1	0.995	3.979E8
	Classification	-19.396	3,286.914	0.000	1	0.995	0.000
	Constant	-1.504	0.295	25.913	1	0.000	0.222
Step 3[c]	Variable 1			6.221	5	0.285	
	Variable 1 (1)	-18.997	3,748.382	0.000	1	0.996	0.000
	Variable 1 (2)	-18.774	9,282.271	0.000	1	0.998	0.000
	Variable 1 (3)	-1.112	4,901.725	0.000	1	1.000	0.329
	Variable 1 (4)	23.632	28,840.325	0.000	1	0.999	1.834E10
	Variable 1 (5)	1.331	4901.725	0.000	1	1.000	3.784
	Classification	-19.211	3,158.566	0.000	1	0.995	0.000
	Gender	18.286	3,748.382	0.000	1	0.996	8.737E7
	Constant	-1.504	0.295	25.913	1	0.000	0.222

Note: a, key in variable (variable 1) in step 1; b, key in variable (classification) in step 2; c, key in variable (gender) in step 3.

there has been no consensus on any ideal treatment method for more complicated VMs, while some studies proposed the idea of multidisciplinary approach [10, 11, 14]. For patients with high-flow type, surgeons should pay much attention to the preoperative preparation and intraoperative procedure in order to prevent any severe uncontrollable bleeding during surgery, especially if they are going to operate on areas where bleeding can occur easily, such as hip and groin. After embolization of the artery, the dilated malformed vascular mass and venous pool would shrink and the tension would decrease, the borders between tumors and normal tissues would become clear, which can make the resection of the tumor easier, and reduce the volume of blood loss [15, 16].

In an effort to find ways to provide better assistance in making suitable treatment plans, we used the new classification to divide VMs in extremities into six groups, which were superficial type, mono-localized type, poly-localized type, extensive type, nerve type and diffuse type [17, 18].

If the lesions of superficial or mono-localized type are at steady state, with small sizes, and don't affect the appearance or impair the function, the regular follow-up can be conducted. The initial management of the disease is conservative, with the aim of reliving pain and swelling. Sclerotherapy, laser treatment and embolization of artery can be beneficial. Surgery should be performed if there is ongoing pain, and malfunction or nerve compression caused by uncontrollable limb swelling. The purpose of the operation is to maximumly remove the lesion, while attention should be paid to avoid injury to adjacent nerves and lymphatic vessels in order to reduce bleeding as much as possible, and to prevent limb ischemia. All these require a detailed preoperative planning and delicate operation. The adjunctive treatment would be necessary. For example, preoperative embolization can be performed

on patients with high-flow type which is adjunctive to the surgery [19]. In the laser treatment, oxyhemoglobin in blood vessel can selectively absorb the color radical in light energy and generate heat locally, thus damaging the affected vessel and removing the lesion [20]. The treatment methods for patients with superficial or mono-localized type in the study were as follows, 80 patients with superficial type and 14 with mono-localized type received laser treatment, 4 with superficial type and 25 with mono-localized type received surgical excision, 17 with mono-localized type received embolization of feeding artery and resection of tumor. Patients were followed up after surgery, which found that improvements in the 84 cases of superficial type (95.24% of improvement rate) and 53 cases with mono-localized type (98.21% of improvement rate). For patients with poly-localized or extensive type, surgeries should be performed if lesions impair the limb function. The type of vascular tumor, and area and depth of the lesion should be determined prior to the operation. Good knowledge of anatomy and tissue structure is required for maximum possible resection of tumor. In cases where muscle transfer can be conducted, the affected muscle should be removed as much as possible; whereas the resection of muscle shouldn't exceed 50% in cases where muscle transfer cannot be performed, so as to keep the function of extremities. A total of 23 patients with poly-localized type and 74 with extensive type were followed up (95.65% and 87.84% of improvement rate, respectively), while 1 case in poly-localized type and 9 cases in extensive type had no improvement. For nerve type in which nerve is affected, the nerve compression should be eliminated, meanwhile blood supply should be maintained in order to avoid nerve ischemia. There were 9 patients with nerve type and 10 with diffuse type, who were followed up after surgery. The improvement rate of nerve type was 55.56% and 4 cases had no improvement; the improvement rate of diffuse type was 80.00% and 2 cases had no improvement. The treatment of VM in diffuse type is still quite difficult. Normally patients with this type are treated with embolization of draining vein by anhydrous ethanol plus sclerotherapy, which is mainly to control the development of disease, and to relieve clinical symptoms. Imaging examination is taken after the surgery immediately, while some scholars suggest taking this test 3 days after surgery [14]. Color Doppler ultrasound can be used selectively followed by CT angiography, but it is believed that MRI is still the best way for evaluating medium- and long-term management of the disease [14].

Disclosure of conflict of interest

None.

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