Peer Review File

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Reviewer A

Comment 1:

This is a well structured manuscript dealing with a new interesting aspect of venous malformations. The study cohort is rather small, but this is due to the rareness of vascular malformations.

In general the term "nidus" should be avoided in the context of venous malformations, because there is a strong association between the term "nidus" and arteriovenous malformations. I would recommend to change this throughout the manuscript.

Reply 1:

Thank you for the comment. By using the term nidus, we wanted to emphasize the key point of the paper, which is the inner structure of venous malformations similar to different nidi described for arteriovenous malformations. However, we do understand the strong association and therefore adapted the term throughout the manuscript.

Changes in the text:

P2; line 5-7: “Not only the drainage, as assessed in the established classification, but also the phlebographic aspect of the internal VM structure itself plays a decisive role.”

P2; line 24-26: “We therefore propose to integrate this parameter of the internal VM structure into the existing classification.”

P3; Key findings: “Phlebographic differentiation into non-lacunar and lacunar structure of venous malformations (VM) is feasible and reliable.”

P3; What is known and what is new? : “Not only the drainage, as assessed in the established classification, but also the phlebographic aspect of the VM itself plays a decisive role.”

P3; What is the implication, and what should change now? : “The internal structure of the VM distinguishing a non-lacunar type (a) and lacunar type (b) should be integrated into the existing classification.”

P 6; line 2-5: “Aim of this study is to validate a revised phlebographic VM classification system by distinguishing a non-lacunar (a) and a lacunar (b) type of internal VM structure as an additional element to take into count the flow patterns, not only of the draining veins, but also of the VM morphology itself.”

P 8; line 12-13: “1. central angioarchitecture of dysplastic venous channels was assessed by visual estimation concerning the presence or absence of lacunar spaces.”

P 9; line 19-21: “The distinction of the central angioarchitecture of dysplastic venous channels into non-lacunar and lacunar type was reliable using a binary visual cut off of more than 80% of the VM angioarchitecture showing lacunar formation or not.”

P 11; line 17-18: “The trend to show higher D-dimers in patients with lacunar VM morphology was interesting, but did not reach statistical significance.”

P 11; line 20-24: “The importance of the internal flow patterns concerning the development of localized intravascular coagulopathy is known and needs to be taken into count if interventional procedures are planned, as they also impact toxicity and efficacy of sclerosants in terms of the endothelial contact surface and the duration and volume needed to fill the VM.”

P 13; line 8-11: “The internal structure of the VM itsself is an important element for interventional embolo-sclerotherpy treatment planning and the differentiation of the central angioarchitecture of

dysplastic venous channels of VM should be integrated into the existing classification in future studies in order to validate this approach."

Comment 2:
Abstract, Key findings etc.:
Good.
Reply 2:
Thank you very much.
Changes in the text:
None.

Comment 3:
Introduction:
p. 4: "If these measures fail to relieve symptoms limiting the patient's quality of life or the VM threatens vital organs or is likely to cause complications such as bleeding or thromboembolism, a treatment aiming for complete occlusion or resection of VM should be planned by an interdisciplinary board of specialists". This sentence is too long and complicated, please adjust.
Reply 3:
You are absolutely right. We adjusted the sentence as indicated below.
Changes in the text:
P 4; line 15-19: "If these measures fail, a treatment aiming for complete occlusion or resection of VM should be planned by an interdisciplinary board of specialists. (4) Not symptoms limiting the patient's quality of life, but also the VM threatening vital organs or causing complications such as bleeding or thromboembolism warrant invasive treatment."

Comment 4:
p. 4: "Not only the drainage, as assessed in the established classification, but also the phlebographic aspect of the VM itself plays a decisive role. The effect of a sclerosant is different in a non-lacunar, small channel VM as compared to ectatic, lacunar VM, in which the effectiveness can be significantly reduced due to lower wall contact and as emptying out of these lacunar veins often is impossible. Combining the procedure using coils can reduce the need for high amounts of the
sclerosing agents and increases the treatment effect."
Is this your personal experience? Does any data/literature exist for this statement? If not, you have to state this.
Reply 4:
Unfortunately there are to our knowledge no publications describing in detail the sclerosation of venous malformations. The statement above is our personal experience, which we now added in the manuscript.
Changes in the text:
P 4-5; line 25-5: "In our experience the effect of a sclerosant is different in a non-lacunar, small channel VM as compared to ectatic, lacunar VM, in which the effectiveness can be significantly reduced due to lower wall contact and as emptying out of these lacunar veins often is impossible. The combination of coils with sclerotherapy has helped us reduce the need for high amounts of the sclerosing agents and increase the treatment effect in large lacunar lesions and ectatic venous channels."

Comment 5:

p. 5: "Aim of this study is to validate the proposal of a revised phlebographic VM classification system by…".

Better: " Aim of this study is to validate a revised phlebographic VM classification system by…".

Reply 5:

We agree and adapted the text accordingly.

Changes in the text:

P 6; line 2-5: “Aim of this study is to validate a revised phlebographic VM classification system by distinguishing a non-lacunar (a) and a lacunar (b) type of internal VM structure as an additional element to take into count the flow patterns, not only of the draining veins, but also of the VM morphology itself.”

Comment 6:

Methods:

p. 6: " Phlebograms were analyzed in a random order by two independent readers..".

Please state the experience in reading phlebograms of vascular malformations of these readers.

Reply 6:

We added the information is the methods section.

Changes in the text:

P 8; line 5-6: “The readers had a 10 and 5 year experience, respectively, in the treatment of venous malformations.”

Comment 7:

p. 8: The third phlebographic study assessment – was this another reading session or were the results of the first and second reading session "combined"? Please clarify.

Reply 7:

The third reading process was a separate reading assessing drainage according to the Puig classification and the VM structure being either lacunar or non-lacunar. We tried to clarify this in the manuscript.

Changes in the text:

P 8; line 21-23: “3. adjusted phlebographic classification, combining assessment of drainage type (I-IV) with additional judgement of the central angioarchitecture of dysplastic venous channels (a or b) in a third and separate reading process.”

Comment 8:

Results:

p. 8: "The distinction of the central angioarchitecture of dysplastic venous channels into non-lacunar and lacunar type was possible for all patients by both readers using a binary visual cut off of more than…"

I think the wording is not appropriate. Was there any possibility for the readers to choose "distinction is not possible"? If yes, you have to state it in the methods section. If not, you have to change the wording.

Reply 8:

Thank you for the remark. There was indeed no possibility not to decide between lacunar and non-lacunar VM structure. We adjusted the sentence accordingly.

Changes in the text:

P 9; line 19-21: “The distinction of the central angioarchitecture of dysplastic venous channels into non-lacunar and lacunar type was reliable using a binary visual cut off of more than 80% of the VM

angioarchitecture showing lacunar formation or not.”

Comment 9:

Discussion:

p. 10 "...we identified the need to assess and integrate the hemodynamic pattern of the central angioarchitecture of dysplastic venous channels itself in addition to the drainage pattern…"…." We propose a schematic and simple adjustment of the current classification by Puig et al. by adding a non-lacunar VM flow-pattern (type Ia, IIa, IIIa, IVa) or a VM lacunar flow-pattern (type Ib, IIb, IIIb, IVb) to the established classification (Figure 3)."

I think the terms "hemodynamic" and "flow pattern" are not perfectly appropriate. I don´t see the hemodynamic information in the first place, the differentiation lacunar vs. non-lacunar is more morphologic, isn´t it?

Reply 9:

Thank you for the comment. We are convinced that the internal hemodynamics are influenced by the VM morphology, but we are indeed describing morphology and internal structure of VMs. We therefore adapted the wording accordingly.

Changes in the text:

P 11; line 3-8: “Phlebographic classification of VMs is mainly dedicated to allow precise treatment planning for embolo-sclerotherapy and better estimation of possible complications due to the need of high volume of sclerosant. We therefore identified the need to assess and integrate the morphologic pattern of the central angioarchitecture of the dysplastic venous channels themselves in addition to the drainage pattern (supplemental online video).”

P 12; line 10-12: “We propose a schematic and simple adjustment of the current classification by Puig et al. by adding a non-lacunar internal VM structure (type Ia, IIa, IIIa, IVa) or a lacunar internal VM structure (type Ib, IIb, IIIb, IVb) to the established classification (Figure 3).”

Comment 10:

p. 11: "Size wise we did not further differentiate VM < 8cm, but as no difference was observed in terms ofinter-reader reliability between the three size groups we defined and even small VMs can be visualized correctly by using a sufficient magnification during image acquisition, this should not impact our results."

This sentence is too long and complicated, please adjust.

Reply 10:

We adjusted the sentence as indicated.

Changes in the text:

P 12-13; line 23-2: “No difference was observed in terms of inter-reader reliability between the three size groups we defined and even small VMs can be visualized correctly by using a sufficient magnification during image acquisition. We therefore think, that the non-differentiation of VM < 8cm, should not impact our results.”

Comment 11:

Figures:

Perfect, especially Fig. 2 and 3!

Reply 11:

Thank you very much again.

Changes in the text:

None.

Reviewer B

General comments

The authors assessed the feasibility of phlebographic differentiation into non-lacunar and lacunar VMs and reliability to distinguish phenotypic subgroups of patients with VM. It's an interesting and well written article.

Suggested considerations for revisions are below.

Comment 12:

Introduction

P.5, L21: "The effect of a sclerosant…often is impossible."

Is this sentence empirical or a generally known fact? If you have any citations, please provide them.

Reply 12:

Thank you for this important remark. Unfortunately there are to our knowledge no publications describing in detail the sclerosation of venous malformations. The statement above is our personal experience, which we now added in the manuscript.

Changes in the text:

P 4-5; line 25-5: "In our experience the effect of a sclerosant is different in a non-lacunar, small channel VM as compared to ectatic, lacunar VM, in which the effectiveness can be significantly reduced due to lower wall contact and as emptying out of these lacunar veins often is impossible. The combination of coils with sclerotherapy has helped us reduce the need for high amounts of the sclerosing agents and increase the treatment effect in large lacunar lesions and ectatic venous channels."

Comment 13:

What are the benefits of classifying VMs into non-lacunar and lacunar VMs except for dosage adjustments? Is it useful for predicting treatment effects? Please describe clinical utilities of the classification.

Reply 13:

Thank you for the comment. We hypothesize that non-lacunar VM might be easier to occlude by sclerotherapy than lacunar lesions due to the better wall contact of the sclerosant in non-lacunar lesions. Unfortunately this was not the focus of the presented study and the study population is too small to draw such conclusions.

We extended the corresponding paragraph in the discussion and added References 21, 22 and 23.

Changes in the text:

P 11; line 10-16: "Although this is done by experience, this might help to interpret treatment effects. Non-lacunar VM is likely to be more easily completely occluded by sclerotherapy than lacunar VM. On the other hand, non-lacunar VM might be more difficult to treat with new approaches such as electro-sclerotherapy, as the electrode positioning might be more challenging. However, a dedicated analysis of treatment outcomes in larger, probably multi-centric cohorts is necessary to clarify these possible implications."

Comment 14:

Fig.1

Please provide all types of direct puncture phlebography, not just type II, so that readers can easily understand them with reproducibility, if possible.

Reply 14:

Thank you for the comment. We agree that it is helpful to show phlebographic examples for all VM types. We adapted Figure 1, which is now showing examples for all the different types of VM structures we propose for the revised classification.

Changes in the text:

Figure 1: Direct puncture phlebography

Exemplary phlebograms of VMs Type I to IV each with non-lacunar (non-lacunar > 80% by visual estimation) and lacunar (lacunar > 80% by visual estimation) type are shown.

Ia) intramuscular VM of the thigh type Ia

Ib) subcutaneous cervical VM Ib

IIa) intramuscular VM of the thigh type IIa

IIb) intramuscular VM of the calf type IIb

IIIa) subcutaneous VM of the foot type IIIa

IIIb) intramuscular VM of the calf type IIIb

IVa) subcutaneous VM of the calf type IVa

IVb) intramuscular VM of the thigh type IVb

Comment 15:

Fig.3

I think the illustration of type IV is different from what defined by Puig et al. They defined type IV as primarily consist of venous ectasia.

Reply 15:

Thank you for this important remark. VM Type IV is effectively defined as ectatic venous channels. We agree that our schematic display of non-lacunar and lacunar structures in this context was not completely adequate. We therefore adapted Figure 3. We hope that with the additions made in Figure 1, it is now sufficiently clear, how we propose to distinguish VM type IVa and IVb.

Changes in the text:

Only Figure 3 was adapted. No changes were made in the corresponding figure legend.