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MRT-basierte Untersuchung der Verteilungsmuster und Charakteristiken von Gefäßanomalien der Becken-Bein-Region

Dissertation zur Erlangung des akademischen Grades

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Referat

Diese Arbeit umfasst die Ergebnisse zweier retrospektiver Studien an einem Datensatz von 378 Patienten mit Gefäßmalformationen in der Becken-Bein-Region, bei denen in einem Zeitraum von sechs Jahren eine hochauflösende 3 Tesla MRT-Bildgebung erfolgte. In der ersten Studie wurde bei Patienten mit venösen Malformationen nach einer Beteiligung des N. ischiadicus gesucht und diese unter besonderer Berücksichtigung von Verteilungs- und Infiltrationsmustern der venösen Malformation systematisch charakterisiert. Die zweite Studie befasst sich mit allen Typen von Gefäßmalformationen hinsichtlich ihrer Prävalenz und Verteilungsmuster am inneren und äußeren Genitale.

Bei 9 % der Patienten mit venösen Malformationen in der Becken-Bein-Region wurde eine Beteiligung des N. ischiadicus in der MRT-Bildgebung nachgewiesen. Es zeigte sich eine Durchmesservergrößerung und T_2-Hyperintensität der betroffenen Nerven. Subepineuriale (52,2 %), subparaneuriale (26,1 %) und kombinierte (21,7 %) Infiltrationsmuster des N. ischiadicus wurden identifiziert. Bei allen Patienten (100 %) mit Nervenbeteiligung fand sich auch eine Beteiligung der Gluteal- oder ischio-cruralen Muskulatur an einer einfachen oder kombinierten venösen Malformation.

Bei 19 % der Patienten mit Gefäßmalformationen in der Becken-Bein-Region wurde eine Beteiligung der Genitalorgane nachgewiesen. Bei 52 % dieser Patienten lag eine kombinierte Beteiligung des inneren und äußeren Genitales vor, bei 33,6 % eine alleinige Beteiligung des äußeren und bei 11,3 % des inneren Genitales. Bei 57,1 % der Patienten mit in der klinischen Untersuchung sichtbaren äußeren Zeichen einer Gefäßmalformation konnte durch die MRT-Untersuchung eine Beteiligung des inneren Genitales nachgewiesen werden.

Aus beiden Studien lassen sich Empfehlungen für die systematische Untersuchung von Patienten mit Gefäßmalformationen in der Becken-Beim-Region mithilfe hochauflösender MRT-Bildgebung ableiten, deren Ergebnisse eine interdisziplinäre Therapie maßgeblich beeinflussen sollten.

Goldann, Constantin: Halle (Saale): MRT-basierte Untersuchung der Verteilungsmuster und Charakteristiken von Gefäßanomalien der Becken-Bein-Region, Univ., Med. Fak., Diss., 16 Seiten, 2022

Report

This dissertation comprises the results of two retrospective studies conducted on a retrospective dataset of 378 patients with vascular malformations in the pelvis and thigh region gathered over a period of six years including high resolution 3 Tesla magnetic resonance (MR) imaging. In the first study, an involvement of the sciatic nerve in venous malformations was investigated. Patterns of malformation distribution and nerve infiltration were characterized systematically. The second study examined the prevalence and distribution patterns of vascular malformations in the genital region.

In 9% of the patients with venous malformations in the pelvis and thigh region an involvement of the sciatic nerve was proven in MR imaging. The affected nerves were enlarged in diameter and showed elevated signals in T_2-weighted sequences. Subepineurial (52.2%), subparaneurial (26.1%) and combined (21.7%) infiltration patterns of the sciatic nerve were identified. In all patients with sciatic nerve involvement, gluteal or hamstring muscles were involved in a simple or combined venous malformation.

In 19% of the patients with vascular malformations in the pelvis and thigh region an involvement of the genital organs was detected. In 52% a combined infiltration of external and internal genital organs was detected. In 33.6% only the external genitals and in 11.3% only the internal genital organs were affected. In 57.1% of patients with externally visible signs of a vascular malformation in the genital region, an additional involvement of the internal genitals was detected.

From both studies, recommendations can be deduced for a systematic examination using high resolution MR imaging in patients with vascular malformations of the pelvis and thigh region as they can have substantial impact on interdisciplinary therapeutic decision making.

Goldann, Constantin: Halle (Saale): MRT-basierte Untersuchung der Verteilungsmuster und Charakteristiken von Gefäßanomalien der Becken-Bein-Region, Univ., Med. Fak., Diss., 16 pages, 2022

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1 Einleitung und Zielstellung

Gefäßmalformationen sind seltene angeborene Erkrankungen des Gefäßsystems, die auf bis dato nicht vollständig verstandene Störungen der Vaskulo- und Angiogenese zurückzuführen sind[1,2]. Sie können sich prinzipiell in allen Körperregionen manifestieren. Von besonderer klinischer Bedeutung sind Gefäßmalformationen in der Kopf-Hals-Region[3], an den Extremitäten[4] und dem Becken einschließlich der Genitalregion[5,6]. Die Einteilung der Gefäßanomalien erfolgt nach der ISSVA-Klassifikation (International Society for the Study of Vascular Anomalies). Diese zuletzt 2018 aktualisierte Klassifikation[7] basiert auf Arbeiten von Mulliken und Glowacki aus den 1980er-Jahren[1], die anhand histologischer Kriterien zwischen Gefäßtumoren und Gefäßmalformationen differenzierten. Die ISSVA-Klassifikation unterscheidet zwischen kapillären, venösen, lymphatischen und arterio-venösen Gefäßmalformationen, die entweder einfach oder kombiniert (d.h. mit mehr als einem Malformationstyp innerhalb einer Läsion, z.B. kapillär-lymphatisch-venös) auftreten können. Ebenso unterscheidet sie zwischen high-flow-Malformationen (z.B. arterio-venöse Malformation) und low-flow-Malformationen (venöse und lymphatische Malformationen)[7]. Charakteristisch für Gefäßmalformationen ist, dass sie im Zuge des kindlichen Wachstums an Größe zunehmen und sich – insbesondere in Gegensatz zu Gefäßtumoren wie dem infantilen Hämangiom – nicht zurückbilden.[8]

Gefäßmalformationen können Teil syndromaler Erkrankungen sein. Beispielhaft sei hier das typischerweise die untere Extremität betreffende Klippel-Trenaunay-Syndrom (KTS) genannt, bei dem kombinierte kapilläre, venöse und lymphatische Malformationen auftreten in Verbindung mit einer knöchernen und Weichteilhypertrophie der betroffenen Extremität[9]. Es wird hervorgerufen durch somatische Mutationen des PIK3CA-Gens[10] ebenso wie das dem KTS ähnliche CLOVES-Syndrom (Congenital lipomatous overgrowth, vascular malformations, epidermal naevi and skeletal anomalies syndrome), für welches jedoch lipomatöse Raumforderungen des Körperstamms charakteristisch sind und bei dem auch arterio-venöse Malformationen neben kapillären, venösen und lymphatischen Malformationen auftreten können[11].

Die klinischen Symptome der Gefäßanomalien variieren je nach Malformationstyp, Lokalisation und Größe. Es gibt Gefäßmalformationen, die lebenslang asymptomatisch bleiben. Zu den typischen Symptomen zählen Schmerzen, Schwellungen, Funktionseinschränkungen und Deformitäten bzw. Dysplasien (z.B. asymmetrisches Wachstum bei arterio-venösen Malformationen) von Extremitäten bzw. von Organen, Fett- und Bindegewebe, Knochen und Muskulatur. Zu den häufigsten mit Gefäßmalformationen assoziierten Komplikationen zählen Thrombophlebitiden, Thrombosen, Thromboembolien, Blutungen und Infektionen.[12] Diese Symptome und Komplikationen können teils massive Auswirkungen auf die Lebensqualität der betroffenen Patienten haben – auch und insbesondere, wenn sensible Bereiche des Körpers wie die Genitalregion betroffen sind.[13]

Gefäßmalformationen sind für die an ihrer Behandlung beteiligten Disziplinen eine diagnostische und therapeutische Herausforderung. Eine ausführliche Anamnese und klinische Untersuchung sind wegweisend zur Diagnosestellung. Zugleich sind es bildgebende Verfahren, die neben einer Einschätzung der räumlichen Ausdehnung der Gefäßmalformation auch für die Therapie bedeutsame Anhaltspunkte liefern. Die Sonographie (einschließlich Doppler) ist bei der nicht-invasiven Ersteinschätzung der Malformation des Malformations-Typs und der Flusscharakteristik von großer Bedeutung. Eine noch umfassendere bildgebende Diagnostik ermöglicht die Magnetresonanztomographie (MRT). Sie erlaubt beispielsweise eine Bestimmung des Typs anhand charakteristischer Merkmale. Insbesondere bei großen oder sehr tiefen Befunden ermöglicht die MRT aussagekräftige Messungen der Befundgröße. Ebenso lassen sich anhand der MRT-Bilddaten die von der Gefäßmalformation betroffenen anatomischen Strukturen identifizieren[14]. Zugleich ermöglicht hochauflösende Magnetresonanztomographie bei hohen magnetischen Feldstärken die Identifikation und Beurteilung feiner anatomischer Strukturen, beispielsweise von Nerven[15], welche von benachbarten oder infiltrierenden Gefäßmalformationen betroffen sein können. Zeitlich aufgelöste MR-Angiographie ermöglicht eine Bestimmung der Flusscharakteristik von Gefäßmalformationen[16,17]. Insgesamt ergeben sich aus den Befunden der MRT-Bildgebung wesentliche Erkenntnisse für die Planung einer interdisziplinären Therapie, welche konservative, interventionelle oder chirurgische Verfahren beinhalten kann[18].

Gegenstand dieser Dissertation ist die retrospektive MRT-gestützte Untersuchung der Verteilungsmuster und Charakteristiken von Gefäßanomalien in der Becken-Bein-Region. Grundlage des zweiteiligen Forschungsvorhabens bildete ein über sechs Jahre (2011 bis 2017) erhobener Datensatz. Dieser beinhaltet hochauflösende Bilddaten aus 3 Tesla MRT-Untersuchungen, klinische Untersuchungsbefunde sowie standardisierte Fragebögen von insgesamt 378 Patienten mit Gefäßmalformationen der Becken-Bein-Region, die sich in o.g. Zeitraum in einem interdisziplinären Zentrum für Gefäßanomalien vorstellten. Im ersten Teil der Arbeit (Anlage A) wurden venöse Malformationen der unteren Extremität mit Infiltration des N. ischiadicus und seinen umgebenden Strukturen untersucht. Im zweiten Teil der Arbeit (Anlage B) erfolgte ein Vergleich der Verteilungsmuster von Gefäßmalformationen in der Genitalregion mit Ergebnissen der klinischen Untersuchung. Es ergeben sich mehrere Fragestellungen:

1. Wie lässt sich eine Infiltration des N. ischiadicus durch venöse Malformationen in der MRT-Bildgebung feststellen und strukturiert und reproduzierbar dokumentieren?
2. Wie häufig findet sich bei Patienten mit venösen Malformationen eine Beteiligung des N. ischiadicus?
3. Weisen den N. ischiadicus infiltrierende venöse Malformationen besondere Infiltrations- und Verteilungsmuster auf? Gibt es Zusammenhänge mit der Beteiligung umgebender anatomischer Strukturen?
4. Hat eine Beteiligung des N. ischiadicus an einer venösen Malformation Einfluss auf Schmerz und Bewegungseinschränkungen als Parameter der Lebensqualität?
5. Wie häufig ist das innere und äußere Genitale von in der Becken-Bein-Region lokalisierten Gefäßmalformationen betroffen?
6. Wie häufig kommen Gefäßmalformationen im Bereich des inneren Genitales vor, die in der klinischen Untersuchung nicht feststellbar, aber durch MRT-Bildgebung nachweisbar sind?

Aus den Ergebnissen beider Veröffentlichungen sollen Handlungsempfehlungen für eine umfassende und qualitativ hochwertige interdisziplinäre Versorgung von Patienten mit Gefäßmalformationen in der Becken-Bein-Region abgeleitet werden.

2 Diskussion

2.1 Darstellung venöser Malformationen mit Beteiligung des Nervus ischiadicus und den umgebenden Muskelgruppen im MRT

Venöse Malformationen mit Nervenbeteiligung wurden bisher nur in Einzelfallberichten[19,20] oder kleineren Fallserien (n < 10) beschrieben[21,22]. Die im Rahmen dieser Promotion durchgeführte Studie[23] (Anlage A) zielte darauf ab, an einem größeren Patientenkollektiv venöse Malformationen mit Nervenbeteiligung nachzuweisen und Verteilungsmuster in Relation zu umgebenden anatomischen Strukturen, insbesondere der Muskulatur, zu charakterisieren. Die Identifikation typischer Infiltrationsmuster der venösen Malformation am N. ischiadicus und seinen Nervenscheidenstrukturen anhand hochauflösender MRT-Bildgebung stellte einen weiteren Forschungsgegenstand dar.

Eine Infiltration des N. ischiadicus, N. peroneus und/oder N. tibialis durch eine einfache oder kombinierte venöse Malformation konnte bei 27 (9,03 %) von 299 Patienten nachgewiesen werden. Bei 19 (82,6 %) Patienten lag ein einseitiger Befund vor, bei 4 (17,4 %) Patienten waren beide unteren Extremitäten von einer venösen Malformation betroffen. Die überwiegende Mehrheit der Patienten berichtete von Schmerzen (95 %) und Bewegungseinschränkungen unterschiedlichen Grades (65 % leichte, 35 % schwere Bewegungseinschränkungen). Nach einem standardisierten Verfahren, das sich an anatomischen Landmarken orientierte, wurden der N. ischiadicus, der N. peroneus und N. tibialis in hochauflösenden 3 Tesla MRT-Bilddatensätzen vermessen. Zusätzlich wurden deren Signaleigenschaften dokumentiert. Die Messdaten zeigten ein konsistentes Muster der Durchmesservergrößerung des N. ischiadicus bei Patienten mit einseitiger Ausprägung der venösen Malformation im Vergleich mit der nicht von der Malformation betroffenen Seite. Die betroffenen Nerven präsentierten sich hyperintens in T_2-gewichteten Sequenzen. Diese Beobachtung ist konsistent mit Beschreibungen einer 2010 publizierten Fallserie von durch Gefäßmalformationen ausgelöster Ischiadicus-Neuropathie[21].

Bei einer Untersuchung der Verteilungsmuster der venösen Malformationen zeigte sich, dass eine Beteiligung des N. ischiadicus bei allen Patienten (100 %) mit einer Beteiligung der glutealen oder ischio-cruralen Muskulatur an der venösen Malformation einherging. Bei einem großen Teil der Patienten (78,2 %) waren sowohl die gluteale als auch die und ischio-crurale Muskulatur von der Gefäßmalformation betroffen. Im Vergleich mit einer anderen Publikation zur Muskelbeteiligung venöser Malformationen[24] stellten wir in unserem Patientenkollektiv (Patienten mit venösen Malformationen mit Beteiligung des N. ischiadicus) eine höhere Prävalenz von venösen Malformationen in der Gluteal- und ischio-cruralen Muskulatur fest. In ihrem 46 Patienten umfassenden Kollektiv, aus welchem allerdings Patienten mit kombinierten oder mit im Rahmen von Syndromen auftretenden venösen Malformationen ausgeschlossen wurden, fanden die anderen Autoren nur bei 13 % der Patienten eine Beteiligung der Glutealmuskulatur und bei 19 % der Patienten Malformations-Anteile in der ischio-cruralen Muskulatur.

Neben den Verteilungsmustern der venösen Gefäßmalformationen in der Becken-Bein-Region wurden dezidiert die Infiltrationsmuster am N. ischiadicus untersucht. Um die in den hochauflösenden MRT-Bilddaten identifizierbaren Infiltrationsmuster am Nerven zu charakterisieren, bot sich eine Einteilung an, die ursprünglich von Neurochirurgen[22] zur präoperativen Abschätzung der Resektabilität von intraneuralen Gefäßmalformationen peripherer Nerven vorgeschlagen wurde. Am häufigsten wurde ein subepineuriales (52,2 %), gefolgt von einem subparaneurialen (26,1 %) Infiltrationsmuster festgestellt. Bei 21,7 % der Patienten wurden kombinierte Infiltrationsmuster mit Überschreitung der Nervenscheiden-Schichten (Epineurium und Paraneurium) festgestellt. In diesem Zusammenhang ist anzunehmen, dass eine systematische Bestimmung der Infiltrationsmuster mittels hochauflösender MRT-Bildgebung einen essenziellen Beitrag zur optimalen interdisziplinären Therapieplanung leisten kann.

Als eine Limitation unserer Studie kann angesehen werden, dass keine histologischen Untersuchungen zur Diagnosesicherung der Gefäßmalformationen durchgeführt wurden. Da jedoch die MRT-Bildgebung in der Diagnose venöser Gefäßmalformationen als nicht-invasive Methode mit einer Sensitivität von 98,9 % und Spezifität von 90 %[25] gut etabliert ist, wurde auf invasive Verfahren zur Diagnosesicherung verzichtet. Grundsätzlich muss bei der Beurteilung der Nervenstrukturen die Möglichkeit einer

Erhebung falsch-positiver Befunde berücksichtigt werden. Mehrere Autoren empfehlen daher, Unterschiede im Durchmesser und bei der T_2-Signalintensität möglichst immer im Seitenvergleich zu bewerten[15,26]. Da bei der überwiegenden Mehrheit der Patienten (82,6 %) eine unilaterale Manifestation einer venösen Malformation vorliegt, ist der Einfluss dieser potenziellen Fehlerquelle jedoch als gering zu bewerten. Als weitere Limitation ist zu berücksichtigen, dass aufgrund des retrospektiven Studiendesigns keine verwertbaren Daten aus neurologischen Untersuchungen (beispielsweise Elektroneurographie) vorlagen. Demgegenüber konnten jedoch Daten zu Schmerzen und Bewegungseinschränkungen ausgewertet werden. Erhöhte Schmerzlevel wurden von allen 19 Patienten mit Nervenbeteiligung berichtet, bei welchen Angaben zu dieser Fragestellung vorlagen. Leichte (13 Patienten, 6 %) bis höhergradige (7 Patienten, 35 %) Bewegungseinschränkungen wurden von allen 20 Patienten berichtet, die Angaben auf einem standardisierten Fragebogen gemacht hatten, mit welchem Patienten mit venösen Malformationen im Rahmen ihrer Erstvorstellung im interdisziplinären Zentrum für Gefäßanomalien um Auskunft zu für die Lebensqualität bedeutsamen Symptomen gebeten werden.

Aus der festgestellten Assoziation von Muskel- und Nervenbeteiligung lassen sich praktische Empfehlungen für die MRT-Befundung bei Gefäßmalformationen mit venöser Komponente in der Becken-Bein-Region ableiten: Bei Infiltration der Gluteal- und ischio-cruralen Muskulatur ist eine Untersuchung des N. ischiadicus in fettgesättigten T_2-gewichteten Sequenzen zu empfehlen. Bei positivem Befund sollte eine regelmäßige Evaluation von Schmerzen und Bewegungseinschränkungen im Rahmen von Follow-up-Untersuchungen erfolgen und eine weitere Abklärung neurologischer Symptome erwogen werden. Die im Rahmen dieser Studie angewandten standardisierten Messungen und bildmorphologischen Charakterisierungen venöser Malformationen mit Nervenbeteiligung demonstrieren, wie eine konsistente und präzise Befundung hochauflösender MRT-Bilddaten zur initialen Diagnosestellung und im Rahmen von Follow-up-Untersuchungen umgesetzt werden kann.

Als Erstautor der Veröffentlichung war ich maßgeblich für das Studiendesign verantwortlich. Die retrospektive Auswertung der MRT-Bilddatensätze und die Datenerhebung anhand klinischer Befunde und Patientenfragebögen wurden von mir eigenständig durchgeführt und durch zwei Fachärzte für Radiologie mit jeweils über 10 Jahren Erfahrung in der bildgebenden Diagnostik und interdisziplinären Behandlung von Gefäßmalformationen qualitätssichernd begleitet. Das Manuskript habe ich eigenständig erstellt und im Diskurs mit den Co-Autoren anhand ihrer zahlreichen hilfreichen Anmerkungen überarbeitet. Sämtliche Abbildungen einschließlich der anatomischen Schemazeichnungen habe ich selbst gestaltet. Den gesamten Publikationsprozess habe ich selbständig verantwortet einschließlich der Beantwortung zahlreicher Kommentare im *peer review* und der entsprechenden Überarbeitungen des Manuskripts. Darüber hinaus organisierte ich mit Unterstützung der Universitäts- und Landesbibliothek Sachsen-Anhalt (ULB) die Finanzierung der *Open Access* Publikation über die Deutsche Forschungsgemeinschaft (DFG) im Rahmen des Projektes DEAL.

2.2 MRT-gestützte Charakterisierung und Untersuchung von Verteilungsmustern von Gefäßmalformationen am männlichen und weiblichen Genitale

Gefäßmalformationen am Genitale können innere (Vagina, Cervix, Uterus und Ovarien bzw. Hoden, Nebenhoden, Prostata und Samenbläschen) und äußere Genitalorgane (Labia majora et minora bzw. Penis und Skrotum) betreffen. In der bisher veröffentlichten Literatur sind bislang Einzelfallberichte und Studien mit bis zu 60 Patienten bekannt, die sich mit Gefäßmalformationen am Genitale beschäftigen. Im Rahmen dieser Promotion wurde eine Studie[27] (Anlage B) unter Nutzung hochauflösender MRT-Bilddaten durchgeführt mit dem Ziel, die Verteilungsmuster der Gefäßmalformationen insbesondere in Hinblick auf eine Beteiligung des inneren und äußeren Genitale zu untersuchen.

Eine Genitalbeteiligung konnte bei 71 von 370 Patientinnen und Patienten (19 %) mit Gefäßmalformationen in der Becken-Bein-Region festgestellt werden. Am häufigsten trat diese bei Patientinnen und Patienten mit kombinierten kapillär-venös-lymphatischen (24/55, 43,6 %), venös-lymphatischen (6/20, 30 %) oder einfachen venösen Malformationen (22/167, 13,2 %) auf. Seltener wurde sie im Zusammenhang mit kapillär-venösen (9/49, 18,4 %) oder arterio-venösen (6/61 Patienten, 9,9 %) diagnostiziert. Insgesamt fallen die Angaben zur Prävalenz höher aus als in vergleichbaren Studien (Vogel *et al.* [6] und Kulungowski *et al.* [5]), welche sich allerdings hinsichtlich ihrer Einschlusskriterien (z.B. Einschluss von Gefäßmalformationen und -tumoren) unterscheiden.

Hinsichtlich der aus den MRT-Bilddatensätzen erhobenen Verteilungsmuster wurde bei der Mehrheit der Patienten (52,1 %) eine kombinierte Beteiligung des inneren und äußeren Genitales festgestellt, gefolgt von einer isolierten Beteiligung des äußeren Genitales bei 36,6 % respektive des inneren Genitales bei 11,3 % der Patienten. Die klinischen Untersuchungsergebnisse wurden mit den MRT-Bilddatensätzen verglichen. Dabei stellte sich heraus, dass bei mehr als der Hälfte der Patientinnen und Patienten (57,1 %), bei denen in der klinischen Untersuchung eine sichtbare äußere Genitalbeteiligung dokumentiert wurde, zusätzlich eine Beteiligung des inneren Genitale durch MRT-Bildgebung festgestellt werden konnte. Die Veröffentlichung einer anderen Arbeitsgruppe[28] zeigte Häufigkeitsangaben zu einer kombinierten Beteiligung des inneren und äußeren Genitales in derselben Größenordnung (45 %). Deren Patientenkollektiv beinhaltet ausschließlich Patienten mit venösen Malformationen und schließt Patienten mit Beteiligung der Unterschenkel aus. Demgegenüber repräsentieren in unserer Studie, in der eine Beteiligung der Unterschenkel kein Ausschlusskriterium darstellt, Patientinnen und Patienten mit venösen Malformationen am Genitale (22/71 Patientinnen und Patienten, 30,9 %) die zweitgrößte Patientengruppe nach den Patientinnen und Patienten mit kombiniert kapillär-venös-lymphatischen Malformationen (24/71, 33,8 %).

Als typische in der Anamnese und klinischen Untersuchung fassbare Symptome konnten Schwellungen (60 % der Patientinnen und 22,6 % der Patienten) und Hautverfärbungen (52,5 % der Patientinnen und 29 % der Patienten) am äußeren Genitale nachgewiesen werden. Diese traten am häufigsten bei Patientinnen und Patienten mit venösen Malformationen (67 %) auf. Eine interessante Nebenbeobachtung stellte die Zunahme der Symptome bei fünf Patientinnen während ihrer Schwangerschaft dar. Ein ähnlicher Zusammenhang wurde bereits in zwei anderen Veröffentlichungen[29,30] beschrieben.

Bei der Bewertung der Studienergebnisse müssen Limitationen berücksichtigt werden, die vorrangig aus dem retrospektiven Studiendesign resultieren. So konnten vorliegende Symptome weniger genau bzw. weniger konsistent erfasst werden als es beispielweise mit einem prospektiven Studiendesign möglich gewesen wäre. Bisherige Veröffentlichungen zu Gefäßmalformationen der Genitalregion beschränkten sich oft auf einen Malformationstyp (z.B. venöse Malformationen[29]) oder ausschließlich das weibliche[29,30] Genitale. Unserer Studie liegt ein hinsichtlich Malformationstyp, Patientenalter und Geschlecht heterogener Datensatz zugrunde. Dies führt zu einer teils eingeschränkten Generalisierbarkeit der Ergebnisse für einzelne Patientengruppen, repräsentiert jedoch den klinischen Alltag in einem interdisziplinären Zentrum, das sich auf die Behandlung von Gefäßanomalien spezialisiert.

Insgesamt zeigen unsere Studienergebnisse, dass bei der Mehrheit der Patienten in der klinischen Untersuchung feststellbare Zeichen und Symptome am äußeren Genitale oft auf eine größere Gefäßmalformation mit Beteiligung des inneren Genitales hinweisen.

Diese Erkenntnisse stärken die Bedeutung der MRT-Bildgebung für die akkurate und umfassende Diagnosestellung von Gefäßmalformationen der Genitalregion, da Informationen über eine mögliche Beteiligung der inneren Genitalorgane, wie sie in der MRT-Bildgebung gewonnen werden, erhebliche Konsequenzen für eine anschließende interdisziplinäre Therapieplanung haben können. Als Empfehlung lässt sich daraus ableiten, dass bei Patienten mit Verdacht auf eine Gefäßmalformation des Genitales mindestens einmal eine MRT-Untersuchung der Becken-Bein-Region erfolgen sollte.

Als Co-Autor war ich an der Studie durch Qualitätssicherung der Datenauswertung und kontinuierliche Mitarbeit am Manuskript beteiligt. Die Entstehung des Manuskripts habe ich über einen Zeitraum von 2 Jahren mit Rückfragen in kollegialen Diskussionsrunden und durch Überarbeitungen des Manuskripts mit zahlreichen Kommentaren und Änderungsvorschlägen begleitet. Weiterhin trug ich durch die Gestaltung der Abbildungen und Tabellen zu einer anschaulichen Präsentation der Ergebnisse bei.

3 Literaturverzeichnis

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4 Thesen

1. Durch hochauflösende MRT-Bildgebung und strukturierte Auswertung anhand anatomischer Landmarken und definierter bildmorphologischer Kriterien kann eine Nervenbeteiligung venöser Malformationsanteile am N. ischiadicus nachgewiesen werden.
2. Bei 9 % der Patienten mit venösen Malformationen in der Becken-Bein-Region konnte eine Beteiligung des N. ischiadicus nachgewiesen werden.
3. Bei venösen Malformationen am N. ischiadicus konnten drei Infiltrationsmuster nachgewiesen werden: Subparaneurial (26,1 %), Subepineurial (52,2 %) und kombiniert (21,7 %).
4. Bei allen (100 %) Patienten mit einer venösen Malformation am N. ischiadicus konnte die Assoziation mit einer venösen Malformation in der ischio-cruralen oder glutealen Muskulatur nachgewiesen werden. Bei 78,2 % der Patienten waren sowohl die gluteale als auch die ischio-crurale Muskulatur betroffen.
5. 95 % der befragten Patienten mit venösen Malformationen mit Beteiligung des N. ischiadicus gaben Schmerzen an. Alle befragten Patienten berichteten von Bewegungseinschränkungen unterschiedlichen Schweregrads.
6. Bei Analyse der MRT-Datensätze wurde bei 52,1 % der von Gefäßmalformationen des Genitales betroffenen Patientinnen und Patienten eine kombinierte Beteiligung des inneren und äußeren Genitales nachgewiesen. Bei 36,6 % war isoliert das äußere bzw. bei 11,3 % nur das innere Genitale betroffen.
7. Bei 57,1 % der Patienten, bei denen in der klinischen Untersuchung Gefäßmalformationen im Bereich des äußeren Genitales festgestellt wurde, konnte durch die MRT-Bildgebung eine Beteiligung des inneren Genitales diagnostiziert werden.

5 Publikationsteil

Anlage A

Goldann C, Helm M, Uller W, Fellner C, Hammer S, Deistung A, Gussew A, Rosendahl J, Wildgruber M, Wohlgemuth WA, Brill R. MR imaging of venous malformations: sciatic nerve infiltration patterns and involved muscle groups. Sci Rep 2020;10(1):14618. doi: 10.1038/s41598-020-71595-6

Anlage B

Helm M, Goldann C, Hammer S, Platz Batista da Silva N, Wildgruber M, Deistung A, Gussew A, Wohlgemuth WA, Uller W, Brill R. Vascular malformations of the female and male genitalia: type and distribution patterns revealed by magnetic resonance imaging. Clin Exp Dermatol 2022;47(1):43-49. doi: 10.1111/ced.14830

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MR imaging of venous malformations: sciatic nerve infiltration patterns and involved muscle groups

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The aim of this retrospective cross-sectional study was to provide an MRI-based examination framework of venous malformations (VMs) infiltrating the sciatic nerve and determine the frequency of nerve infiltration patterns and muscle involvement in correlation to the patients' quality of life. Pelvic and lower limb MR images of 378 patients with vascular malformations were examined retrospectively. Pain levels and restriction of motion were evaluated with a questionnaire. Cross-sectional areas of affected nerves were compared at standardized anatomical landmarks. Intraneural infiltration patterns and involvement of muscles surrounding the sciatic nerve were documented. Sciatic nerve infiltration occurred in 23/299 patients (7.7%) with VM. In all cases (23/23; 100%), gluteal or hamstring muscles surrounding the nerve were affected by the VM. Infiltrated nerves were enlarged and showed signal alterations (T2-hyperintensity) compared to the unaffected side. Enlarged nerve cross-sectional areas were associated with elevated pain levels. Three nerve infiltration patterns were observed: subepineurial (12/23; 52.2%), subparaneurial (6/23; 26.1%) and combined (5/23; 21.7%) infiltration. This study provides a clinically relevant assessment for sciatic nerve infiltration patterns and muscle involvement of VMs, while suggesting that VMs in gluteal and hamstring muscles require closer investigation of the sciatic nerve by the radiologist.

Abbreviations

VM	Venous malformation
ISSVA	International society for the study of vascular anomalies
VMCM	Cutaneomucosal venous malformation
CLVM	Capillary-lymphatic-venous malformation
STIR	Short tau inversion recovery
TSE	Turbo spin echo
TWIST	Time-resolved angiography with interleaved stochastic trajectories

Vascular anomalies of the lower limb are an uncommon diagnosis, which begins with an early onset in childhood or adolescence. These anomalies are congenital, grow at the same rate as the child and do not regress over time[1]. The diagnosis is primarily made based upon physical examination and the patient's history of malformations with subcutaneous parts. However, imaging with ultrasonography and magnetic resonance imaging (MRI) plays an important role in confirming the diagnosis, as well as evaluating the size and extent of the malformation, because physical examinations tend to underestimate these factors[2]. Deeply seated malformations without subcutaneous portions may only be detectable in MR images.

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In 1982, a classification was introduced by Mulliken et al. to distinguish hemangiomas from vascular malformations with reference to histological features and findings during the physical examination and is still prevalent today[1]. Based on their work, the International Society for the Study of Vascular Anomalies (ISSVA) established a standardized nomenclature comprising all vascular anomalies and tumors. The classification was last updated in 2018[3]. Until now, a large number of musculoskeletal radiologists do not use the ISSVA classification in clinical practice[4]. According to the ISSVA classification[5], low-flow vascular malformations incorporate simple venous and combined malformations of venous and lymphatic type, with or without capillary components.

Venous malformations (VMs) represent a large group within vascular malformations[6], especially in the extremities: In a study of 5,621 patients, 36.8% of all vascular anomalies were venous malformations. 48.3% of venous and 63.3% of combined venous-lymphatic malformations occurred in the extremities[7].

A VM in the lower limb can infiltrate the sciatic nerve, resulting in sciatic neuropathy with subsequent leg pain and restrictions in motion. Previous research has predominantly consisted of case reports[8,9]. For the current study, we conducted a systematic approach to identify and characterize VM which infiltrate the sciatic nerve and its surrounding muscles, as well as investigated the applicability of a radiological classification system for intraneural vascular anomalies proposed by Prasad et al.[9] in our group of patients.

Materials and methods

Approval by the Regensburg University Institutional Review Board (IRB) was obtained (ethics vote number 18-886-104). Written informed consent was waived by the IRB due to the retrospective and non-invasive nature of the study. The study was conducted in accordance with the Declaration of Helsinki. The anonymization of patient data in the research process ensured data protection in accordance with the European General Data Protection Regulation.

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Study participants. We retrospectively analyzed the MRI examinations and clinical records of 378 patients with vascular malformations of the pelvis and thighs. The data was obtained over a 6-year time period (2011 to 2017) at the patients' initial referral to an interdisciplinary treatment center for vascular anomalies. Inclusion criteria were the presence of a simple or combined VM in the sciatic, peroneal and/or tibial nerve visible in MRI. In case of reduced image quality due to motion artefacts, patients were excluded if the sciatic nerve was not discernable at all predefined landmarks and therefore the nerve's diameter could not be measured. Additionally, patients with incomplete image acquisition (e.g. missing MR sequences, see section "Image Acquisition") were excluded. The application of the above-mentioned criteria is shown in the research flowchart (Fig. 1).

Quality of life. In order to record patient symptoms, in particular, pain and restriction of motion, we had the patients complete a standardized disease-specific questionnaire. Pain intensity was reported on a 0-to-10 Visual Analog Scale. Restriction of motion was investigated using five-point Likert scales in order to quantify the patients' ability to perform demanding tasks like climbing stairs as well as common daily activities. According to the statements, their impairment was categorized as "no", "mild" or "severe" restriction in movement.

Image acquisition. All MR images were acquired using a 3 T MR scanner (Magnetom Skyra, SIEMENS Healthineers, Erlangen, Germany). The standardized imaging protocol contained the following sequences: T2-weighted Short Tau Inversion Recovery (STIR) in the axial plane, T2-weighted turbo-spin echo (TSE) in the axial plane, T2-weighted STIR in the coronal plane, T1-weighted turbo-spin echo in the coronal plane and 3D time-resolved MR angiography with interleaved stochastic trajectories (TWIST) before injection of contrast agent, T1-weighted high-resolution 3D gradient echo with spectral fat saturation (volumetric interpolated breath hold examination, VIBE) after injection of Gadobutrol (Gadovist, Bayer, Leverkusen, Germany) adjusted to the patient's body weight.

Analysis. The author and two radiologists experienced in the field of vascular anomalies interpreted the anonymized MR images in consensus. The extent of the VM itself as well as the infiltrated muscles were documented. To assess morphological differences of the sciatic nerve among affected and healthy limbs, the cross-sectional areas of the nerves were measured in the axial plane. To address anatomical variations of the sciatic nerve, all cross-sectional areas were determined for both thighs at predefined anatomic locations, as illustrated in Fig. 2:

(1) proximal landmark at the ischial tuberosity,
(2) intermediate landmark in the sectional image of equal distance between landmark 1 and 3,
(3) landmark at the division of the sciatic nerve (into tibial and peroneal nerve),
(4) proximal tibial nerve, and
(5) proximal peroneal nerve.

We also used this nomenclature of landmarks to describe the extent of the sciatic nerve's involvement in the vascular anomaly. The nerves' cross-sectional area, A, was approximated with an ellipse formula incorporating two nerve diameter measurements: $A = \pi \times \frac{d_1}{2} \times \frac{d_2}{2}$. The major axis of the ellipse is defined as d_1, representing

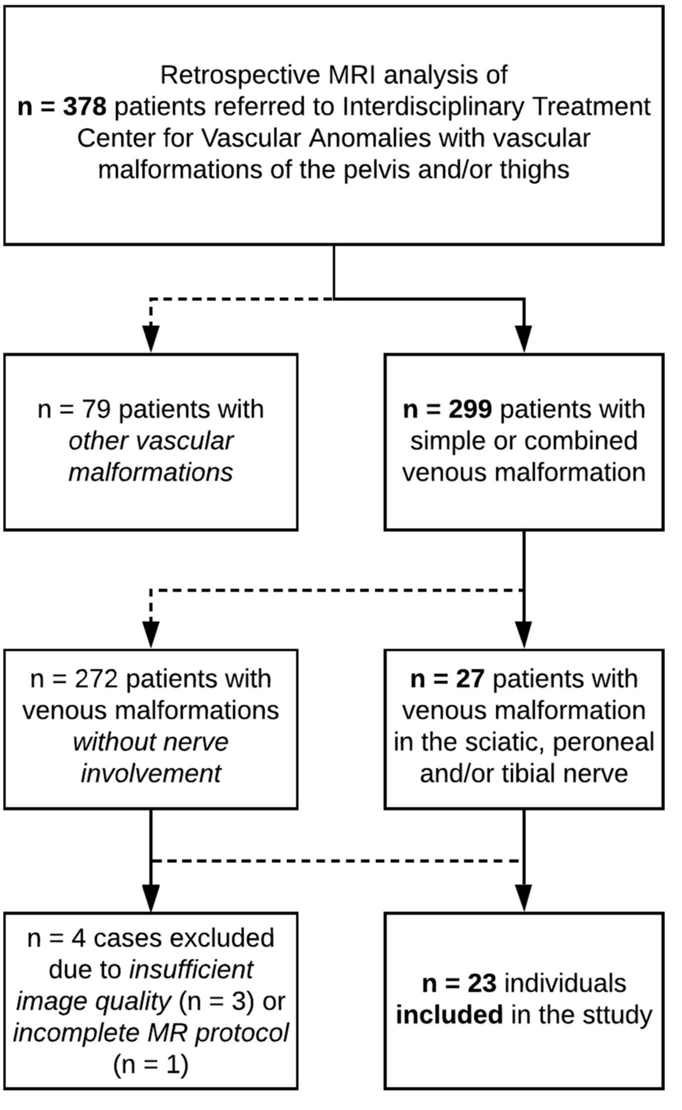

Figure 1. Research flowchart of this study.

the maximal nerve diameter. The minor axis, d_2, is the second measurement orthogonal to d_1. To ensure inter-individual comparability of patients with unilateral anomalies, ratios between the cross-sectional nerve areas of the affected and healthy thigh, q, were computed and considered in the analyses:

$$q = \frac{A_{affected}}{A_{unaffected}}.$$

In affected areas within the sciatic nerve, the presence of a VM was confirmed on the basis of the following MRI criteria. VMs show intermediate heterogenous signals in T1-weighted sequences and high signals in STIR and T2 sequences. The absence of flow voids is characteristic of low-flow malformations. Hypointense areas are caused by thromboses or phleboliths[10]. Fluid–fluid levels can be attributed to hemorrhage or elevated protein content[11]. Gadolinium enhancement in venous malformations is slow and gradual in comparison to arterio-venous malformations, which exhibit early and fast filling with a contrast agent[11]. In macrocystic lymphatic malformations, Gadolinium enhancement can be observed only at the rim and the septa[2,12], whereas microcystic lymphatic malformations usually show no significant enhancement[2]. Capillary malformations occur at skin level. Thus, only a thickening of skin or subcutaneous tissue can occasionally be observed in MR images[2,13].

For an anatomical description, we refer to an anatomic framework proposed by Prasad et al. (2016) to analyze nerve involvement[9].

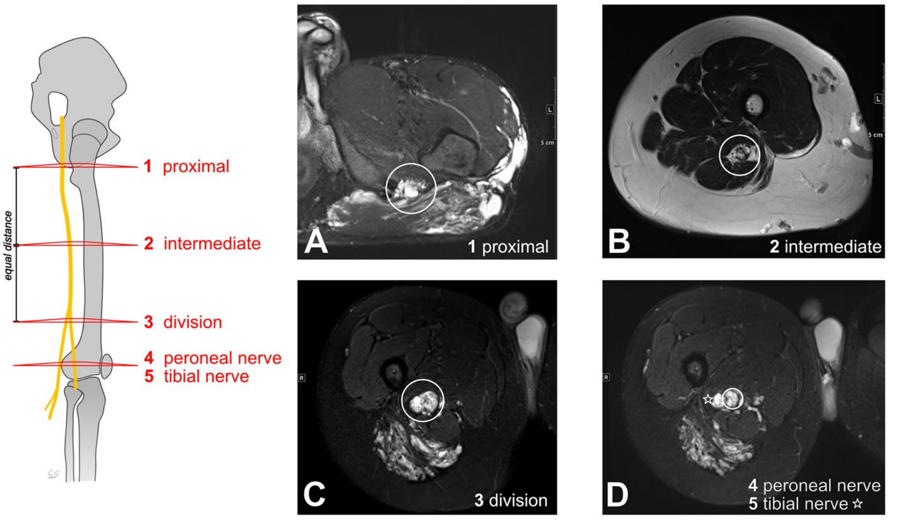

Figure 2. Illustration of the landmarks 1–5 used for measuring nerve cross-section areas and examples of corresponding MR images. All images show venous vascular anomalies with a subepineurial nerve involvement pattern. (**A**) Axial T2 STIR: Sciatic nerve at landmark 1. (**B**) Axial T2 TSE: Sciatic nerve at landmark 2. (**C**) axial T2 STIR: Sciatic nerve at landmark 3 (division into tibial and peroneal nerve). (**D**) axial T2 STIR: Peroneal (landmark 4) and tibial nerve (landmark 5) distal to their division. The peroneal nerve is highlighted with a circle, the tibial nerve with an asterisk.

Results

Out of 299 patients (204 females; mean age 23.8 ± 18.2 years) with a simple or combined VM of the pelvis and/or thighs, we found 27 (9.03%) with an involvement of the sciatic, peroneal and/or tibial nerve. Three cases were excluded due to insufficient image quality caused by motion artefacts. One case was excluded because the MR protocol did not encompass all required sequences. 23 individuals (7.7%) (10 females; mean age 22.3 ± 12.2 years) met our previously defined inclusion criteria. Of these 23 patients (Table 1), 4 (17.4%) had a bilateral and 19 (82.6%) a unilateral (9 left- and 10 right-sided) VM. The study population encompassed 17 adults (mean age 27.8 years), and 6 children (< 18 years; mean age: 6.5 years). Among eight patients with simple VMs, one individual was diagnosed with PTEN-Hamartoma-Tumor syndrome and another one with a Cutaneomucosal Venous Malformation (VMCM). Combined VMs were identified in 15 patients. Within the combined VM group of patients, nine had capillary-lymphatic-venous malformations (CLVMs), which included one patient with CLOVES-syndrome and another with Klippel-Trénaunay-syndrome.

None of the patients included in the study had undergone previous interventions or surgery of the sciatic nerve.

20 of the 23 patients completed the standardized disease-specific questionnaire. 19 patients provided pain responses, resulting in a median pain level of 7 (Range 1–9) on a 0-to-10 visual analog scale. 20 patients indicated that they experienced restrictions in motion to varying degrees: Mild limitations were reported by 13 patients, mainly occurring under heavy exertion. The other seven patients reported severe restrictions in motion occurring even during light daily activities.

In the MR images across all patients, an intraneural manifestation of the malformation was observed in at least one of the defined landmarks. The median ratio of the nerve's cross-sectional areas on the involved side compared to the noninvolved side was $q > 1$ at all measured points among the 19 patients with a unilateral manifestation. A cross-sectional area ratio of $q > 1$ implies that the affected nerves presented enlarged in MR images (Table 2).

An association of the cross-sectional area ratio q and the reported pain level (Fig. 3) was found.

Dilated intraneural vessels were clearly detected in the T2-weighted (Fig. 4) and T1-weighted Gadolinium enhanced sequences in 19 of the 23 patients (82.6%). In all 23 patients, the local findings showed strong hyperintensity of the affected sciatic, peroneal or tibial nerves in fat-saturated T2-weighted sequences. In patients with combined slow-flow malformations, we found that only the venous portions infiltrated the sciatic nerve. Lymphatic or capillary portions of these malformations, when present, did not involve the affected nerves in any patient. Capillary portions of combined malformations, which were found in physical examination, occurred only at the skin level and therefore, did not involve structures of the sciatic nerve.

We describe the intraneural infiltration patterns following the anatomical framework proposed by Prasad et al.[9] (Fig. 4). In line with their classification system, 2 of our patients (8.6%) showed combined extraneural-subparaneurial, 3 (13.04%) combined subparaneurial-subepineurial, 6 (26.1%) subparaneurial and 12 (52.2%) subepineurial infiltration patterns of the sciatic, peroneal and/or tibial nerves. Across all of the aforementioned landmarks of the sciatic and tibial nerves, subepineurial infiltrations were predominantly observed. The peroneal nerve (landmark 4) was the exception, with mainly subparaneurial infiltration patterns (for a detailed list, see

Pat. No	Affected nerve sections (Fig. 1)	Affected side	Clinical classification	MRI diagnosis at nerve, nerve infiltration pattern[9]	Muscle involvement	Nerve cross-sectional ratio q of all affected sections (median)	Pain (VAS)	Restriction in motion
1	1 to 5	b	CVM	VM, SE	B		1	Mild
2	1, 2	l	VM	VM, SE	B	2.84	7	Mild
3	1 to 3	l	CLVM	VM, SP	B	5.63	N/A	N/A
4	1 to 5	r	CLVM	VM, SP-SE	B	3.76	5	Mild
5	1	l	VM	VM, SE	G	4.37	8	Severe
6	2 to 5	l	CLVM	VM, EN-SP	B	3.59	9	Severe
7	3, 4	r	CVM	VM, SE	B	3.74	1	Mild
8	1 to 4	l	VM	VM, SE	B	3.95	2	Mild
9	2 to 4	r	CLVM	VM, SP-SE	B	3.14	N/A	N/A
10	1, 2	b	VM	VM, SP	B		3	Mild
11	2, 3	r	LVM	VM, SE	B	2.99	4	Mild
12	3, 4	b	CLVM	VM, EN-SP	B		7	Severe
13	1 to 5	r	VM	VM, SP	B	4.91	8	Mild
14	1 to 5	l	CLVM	VM, SP	B	4.60	7	Mild
15	1 to 4	r	CLVM	VM, SP	B	3.60	3	Mild
16	1, 2	l	VM	VM, SE	G	9.10	N/A	N/A
17	1, 2	b	VM	VM, SE	B		7	Mild
18	1, 2	r	CLVM	VM, SP-SE	B	4.07	8	Severe
19	1 to 3	r	VM	VM, SE	H	8.25	7	Severe
20	1 to 3	r	LVM	VM, SE	B	10.16	8	Severe
21	1	l	CVM	VM, SP	H	4.08	6	Mild
22	1 to 3	l	LVM	VM, SE	H	3.17	3	Mild
23	1, 2	r	CLVM	VM, SE	B	4.90	N/A	Severe

Table 1. Information per patient. The nerve cross-sectional ratio q is only calculated for patients with unilateral VM manifestation. Affected nerve section refers to the predefined landmarks, as depicted in Fig. 1. Affected side: *b* both, *l* left, *r* right. Muscle involvement: *B* both gluteal and hamstring muscles, *G* gluteal muscles only, *H* hamstring muscles only. Nerve infiltration pattern following the nomenclature of Prasad et al.[9]: *SE* subepineurial, *SP* subparaneurial, *EN* extraneural. *VAS* visual analog scale. *N/A* not available.

Table 2). The paraneurium (Fig. 4C) is the tissue that allows nerve motility and establishes a connection to the structures surrounding the nerve[14].

With respect to the muscles surrounding the sciatic nerve (Fig. 5), we found certain muscles groups to be affected by the VM (Table 1). In all 23 patients, gluteal and/or hamstring muscles were involved: 18 patients (78.2%) had both gluteal and hamstring involvement, 3 (13%) patients had exclusive involvement of the hamstring muscles and 2 (8.7%) individuals had sole involvement of the gluteal muscles. In 12 of 12 cases (100%) of extensive VMs (VM visible at more than 3 landmarks) infiltrating the nerve, both the gluteal and hamstring muscles were involved in the VM (Fig. 6). The hamstring muscles (biceps femoris, semimembranosus and semitendinosus) were involved in 21 of 21 patients (100%) with a VM in intermediate and distal parts of the sciatic nerve (landmark 2 to 5). The gluteal muscles were affected in 15 of 18 patients (83.3%) with a proximal sciatic VM (landmark 1).

In one case (Patient No. 21), a proximal infiltration (landmark 1) of the sciatic nerve was diagnosed without accompanying involvement of the gluteal muscles, but the VM was present in the subcutaneous fat and connective tissue.

Discussion

This data suggests an association of high clinical relevance: Sciatic nerve involvement consistently co-occurs with extensive intramuscular manifestations of venous malformations in hamstring and/or gluteal muscles. We assume that the knowledge of this association can facilitate the assessment of lower extremity VMs in regards to nerve involvement. Taking a closer look at the neural structures, the enlargement of the affected nerve in comparison to the healthy side provides a highly consistent pattern suitable for detecting nerve involvement. The accompanying hyperintensity of the neural tissue and its surrounding structures in T2-weighted images can be regularly observed and interpreted as sign of irritation and inflammation.

The prevalence of VMs in lower extremity muscles has been reported by Hein et al.[15]. Among 46 individuals, they found 6 patients (13%) with the gluteal muscles and 9 patients (19%) with the hamstring muscles involved in simple VMs. In their collective, they reported less involvement of these muscle groups in comparison to our results. The difference can be explained by our selection of cases with nerve involvement and the inclusion of not only simple, but also combined VMs and syndromes.

Landmark	n	Cross-sectional area A: Median (in cm²) Affected side	Unaffected side	Ratio q: Median (25th; 75th percentile)
(1) Sciatic nerve: proximal	**15**	**1.33**	**0.33**	**4.08 (2.96; 6.8)**
Extraneural	2	1.08	0.8	
Subparaneurial	7	1.32	0.36	3.76 (2.0; 6.14)
Subepineurial	9	1.35	0.36	3.37 (2.97; 8.11)
(2) Sciatic nerve: intermediate	**16**	**0.99**	**0.25**	**3.77 (2.79; 5.78)**
Extraneural	1	[0.83]	[0.1]	[8.51]
Subparaneurial	8	0.83	0.17	3.77 (3.73; 5.08)
Subepineurial	9	1.33	0.28	3.25 (2.45; 6.45)
(3) Sciatic nerve: division	**12**	**0.88**	**0.22**	**3.89 (3.09; 5.73)**
Extraneural	1	[0.57]	[0.15]	[3.89]
Sub-paraneurial	5	0.91	0.22	3.97 (3.61; 5.82)
Subepineurial	7	0.84	0.25	3.17 (2.94; 5.23)
(4) Peroneal nerve	**7**	**0.30**	**0.08**	**3.94 (2.86; 4.82)**
Extraneural	1	0.15	0.07	[2.08]
Subparaneurial	5	0.3	0.09	3.89 (3.05; 4.46)
Subepineurial	4	0.23	0.07	4.55 (4.0; 4.92)
(5) Tibial nerve	**5**	**0.45**	**0.16**	**3.29 (2.64; 4.49)**
Extraneural	1	0.3	0.09	[3.29]
Subparaneurial	3	0.53	0.16	3.55 (2.34; 4.79)
Subepineurial	4	0.27	0.11	[3.88]

Table 2. List of cross-sectional areas of affected and healthy limbs in 19 patients with unilateral manifestation, providing the median cross-sectional area and the median ratios q of affected and unaffected side. Values are given for each pre-defined landmark and broken down by affected anatomical compartments according to[9]. Note that VMs can manifest in more than one anatomical compartment of the nerve. Numbers in square brackets indicate that only 1 patient contributed.

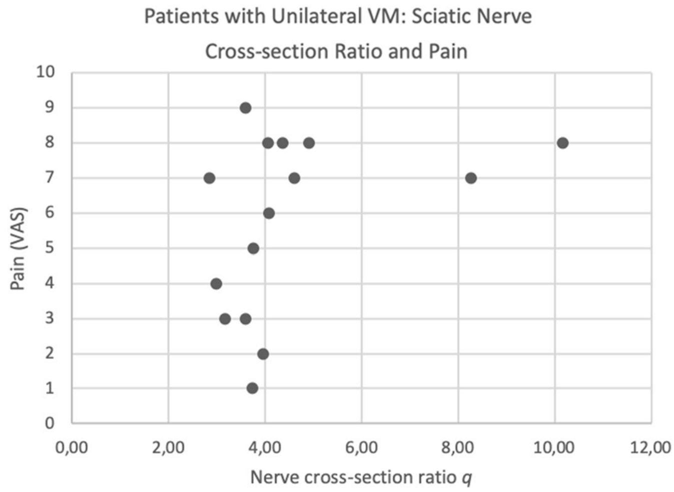

Figure 3. Association of cross-sectional area ratio q and pain level. *VAS* Visual analog scale.

Van Gompel et al.[8] presented a case series of vascular malformations (2 of 4 patients with a VM) causing sciatic neuropathy. Similar to our findings, their MR examinations showed enlarged and hyperintense sciatic nerves in T2-weighted images. In one patient, at the 6-month follow up after external and internal neurolysis, the nerve showed decreased hyperintensity in T2[8]. Examining the provided images of this previous work, within the limitations of image quality, we categorized their finding as a subparaneurial venous malformation.

A radiological classification system based on an anatomic framework was proposed by Prasad et al.[9] with the intent to facilitate surgical decision-making. While presented for nine patients with intraneural lesions, their system has also proven applicable to our patient cohort. Our findings strongly confirm their statement that subepineurial manifestations of VMs are accompanied by nerve enlargement and signal hyperintensity in

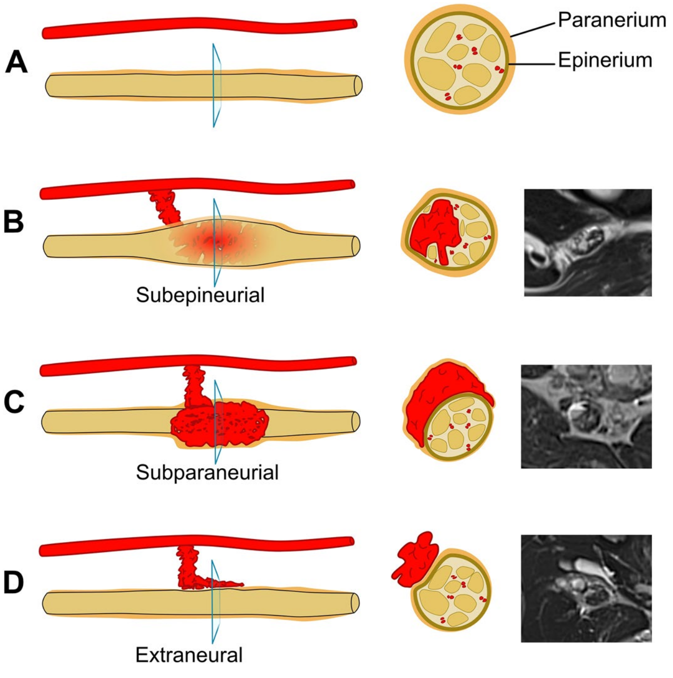

Figure 4. Infiltration patterns of vascular anomalies in neural tissue following the classification of Prasad et al.[9]. The left and middle row show schematic illustrations of infiltration patterns in longitudinal and cross-sectional view, respectively. The right row exemplarily displays the corresponding infiltration patterns observed on axial T2-weighted images. (**A**) Normal nerve without any infiltration by a vascular anomaly. (**B**) VM with subepineurial infiltration of the sciatic nerve. (**C**) VM with subparaneurial infiltration of the tibial nerve. (**D**) VM with extraneural manifestation around the sciatic nerve.

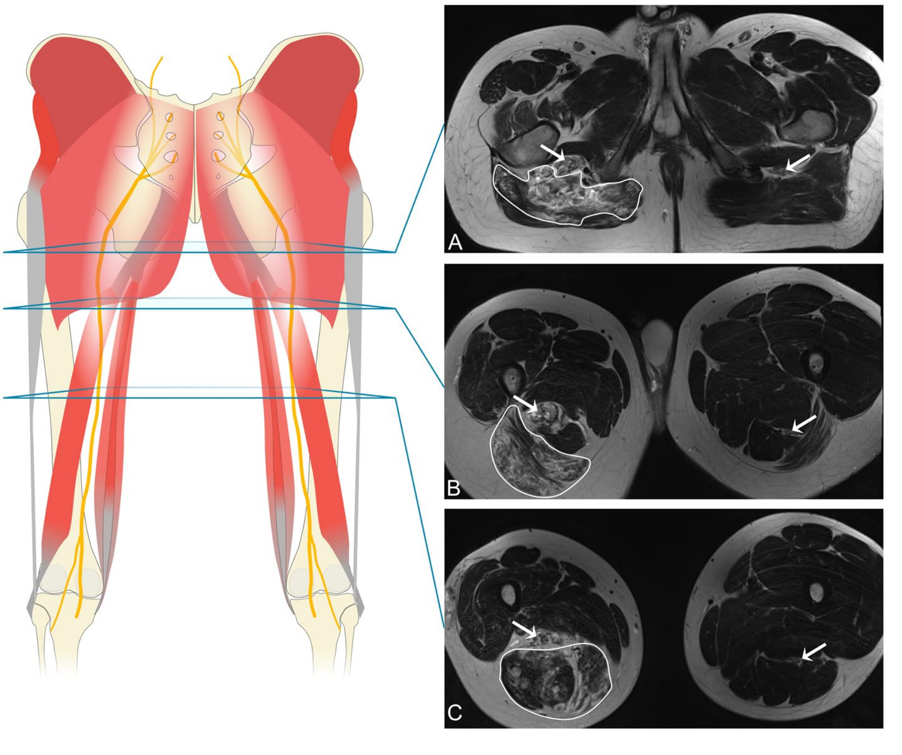

Figure 5. Widespread venous malformation of the right thigh infiltrating into gluteal and hamstring muscles and the sciatic nerve. (Patient 20). The sciatic nerve is marked with an arrow on the affected and healthy side. Outlined areas signify infiltrated muscles. (**A**) All gluteal muscles infiltrated by the VM. (**B**) Distal portion of gluteus maximus and proximal hamstrings infiltrated by the VM. (**C**) Hamstring muscles (semimembranosus, semitendinosus, biceps femoris) infiltrated by the VM.

Figure 6. Extensive venous malformation in a 39-year old female patient. The composed T2-weighted STIR image in the coronal plane shows a subparaneurial involvement of the sciatic nerve (n), the gluteal (m) and hamstring (h) muscles, the rectum (r), the genital area (g) and the subcutis of the right thigh (ellipse).

T2-weighted images[9]. Furthermore, we assume that the classification by Prasad et al. is not limited to the surgical decision-making process and can also be applied to planning and follow-up of conservative or interventional treatment.

We are well aware of the limitations of our study. There was no histological confirmation of the diagnosis. However, since physical examination, diagnostic ultrasound and MRI guide the treatment of VMs[13,16], we decided not to conduct biopsies in our study. MRI is well established in the diagnosis and long-term management of VMs, with a sensitivity of 98.9% and a specificity of 90% that are comparable to Phlebography (sensitivity 97.3%, specificity 91.7%)[17]. MR imaging can show the dimensions of a VM and the involvement of nearby structures and additionally categorize VMs and differentiate them from other malformations[6]. The excellent contrast and resolution of 3 T MR neurography allows the appraisal of fascicular patterns and perineural structures[18]. Still, imaging and interpretation pitfalls should be kept in mind throughout the diagnostic process. T2 hyperintensity and the difference in thickness of the affected nerve have to be verified by comparison to the healthy side in order to rule out false-positives[19,20]. This limitation has to be kept in mind in the examination of bilateral manifestations of VMs. However, in our cohort, unilateral manifestations of VMs in the lower extremity occur more often than bilateral manifestations. Therefore, we assume that the consequences of this interpretation pitfall are marginal. Neurological diagnostic data (i.e. electroneurography) were not collected in our patient analysis. Instead, we followed clinical symptoms using a standardized assessment of pain and restriction in motion. In this context it should be mentioned that nerve lesions can be detected and localized in MR imaging with high spatial resolution[21] at an early stage before changes appear in electroneurography or electromyography[22]. Therefore, we advise that MRI findings of nerve involvement are an indication for additional neurological examination to prevent aggravation of pain or neurological deficits. Since multiple case reports indicate that nerve-associated vascular anomalies may have an effect on electromyographic findings[8,23], we anticipate that further research in this field is necessary.

Conclusion

This study provides a clinically applicable and highly relevant approach to the MRI-based assessment of simple and combined venous malformations (VMs) in the lower extremity. We strongly recommend all clinicians examining MR images of venous malformations to be vigilant about the possible involvement of nerve structures. The highly consistent pattern of involvement of the gluteal and hamstring muscles should be used to guide the radiologist to a closer examination of the nerve structures. Muscle involvement, differences in nerve diameter, hyperintensity of the nerve in fat-saturated T2-sequences and dilated intraneural vessel structures are indicators of nerve infiltration. Consequently, intraneural findings in MR imaging can influence decisions towards further neurological diagnosis and may even determine the feasibility of interventions. They also may call for an increased frequency of follow-up examinations (e.g. every six months) in the long-term therapeutic relationship. We believe that the observation of the nerve's morphology in MRI should be part of any conservative management or interventional treatment of venous malformations affecting the lower extremity. Meticulous diagnosis and follow-up require a comprehensive framework for the morphologic description and measurements, as presented in this study.

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Author contributions

C.G. was the primary author of the manuscript. C.G. and R.B. are responsible for the study design. W.U. and S.H. performed literature review and data analyses (dataset of 378 MRI). C.F., A.D. and A.G. (MRI physicists) created and optimized the MRI protocols and provided substantial input to the method descriptions in the manuscript. C.G., M.H. and M.W. created the figures and tables. C.G. created the drawings in the figures. J.R., M.W. and W.A.W. provided assistance to the study design. All authors reviewed and approved the manuscript.

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Competing interests

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Additional information

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Original article

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Vascular malformations of the female and male genitalia: type and distribution patterns revealed by magnetic resonance imaging

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Summary

Background. Vascular malformations of the genitalia often go undetected in clinical examination. These vascular malformations can cause a variety of clinical symptoms such as swelling, pain and bleeding.
Aim. To characterize the distribution patterns of genital vascular malformations using magnetic resonance imaging (MRI) and to correlate these patterns with clinical findings in order to guide diagnostic decisions.
Methods. A retrospective analysis of MRIs of the pelvis and legs in 370 patients with vascular malformation was performed to determine the involvement of the internal and external genitalia.
Results. In 71 patients (19%), genital involvement could be identified by MRI. Of these, 11.3% (8 of 71) presented with internal involvement, 36.6% (26 of 71) with external involvement and 52.1% (37 of 71) with both internal and external involvement. Over half (57.1%) of the 49 patients with visible external genital signs detected during a clinical examination had additional internal genital involvement.
Conclusions. Genital involvement is a common finding in patients with vascular malformation of the legs and/or pelvis. Based on our data, we recommend MRI of the legs and pelvic region in patients with externally visible signs of a vascular malformation of the external genitalia in order to exclude additional internal involvement.

Introduction

Vascular malformations are rare, congenital and lifelong diseases caused by mesenchymal and angiogenesis disorders during embryogenic development.[1] Vascular malformations can affect various body parts, such as the head and neck, extremities and pelvis, as well as the genital area.[2–4] Depending on the specific blood flow characteristics, vascular malformations can be differentiated into fast-flow lesions such as arteriovenous malformations (AVMs) and slow-flow lesions such as venous malformations (VMs).[5] According to the classification by the International Society for the Study of Vascular Anomalies (ISSVA), vascular malformations can be subdivided into two subtypes: simple (e.g. isolated VMs) and combined [e.g. venous lymphatic malformation (VLM)].[6] Clinical examination and medical history are the primary diagnostic tools for assessment of vascular malformations.[1] Various imaging techniques such as magnetic resonance imaging (MRI), computed tomography, ultrasonography and angiography can be used to confirm the diagnosis.[7]

In this study, we focused on vascular malformations with genital involvement. This presentation is relatively rare[8–10] but represents an important clinical

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finding as it can cause pain, swelling, bleeding, urinary dysfunction, reduced fertility and pregnancy complications, along with subsequent psychological challenges.[7,11–14] For assessment of the internal genitalia, additional imaging such as MRI has proven valuable.[10,15,16]

The main objective of this retrospective study was to determine the prevalence of internal genital involvement in cases with visible signs of malformation of the external genitalia in order to guide clinicians in further diagnostic decisions. A secondary objective was to assess the types of malformation and the prevalence of genital involvement in patients with vascular malformations in the legs and/or pelvis. We focused on the effect of using MRI to detect genital vascular malformations by comparing the outcomes of MRI with the detection rates achieved by clinical examination (clinical findings) alone.

Methods

The study was reviewed and approved by the ethics committee of Regensburg University (approval no. 18-886-104), and the study was exempt from informed consent.

Study design and participants

This was a cross-sectional, explorative, retrospective study of patients with vascular malformations in the legs and/or pelvis, assessed during the period November 2011 and February 2018 in the tertiary care interdisciplinary Vascular Anomalies Centre (VAC) of the University of Regensburg. The study enrolled 378 patients (130 male, 248 female; mean $\pm$ SD age 27.8 ± 17.3 years, range 1.4–63.9 years; 141 patients were aged < 18 years).

Magnetic resonance imaging

At their initial referral, each patient underwent MRI according to a standardized protocol, covering the entire lower body from the pelvis to the feet (independent of the size of the vascular malformation). Standardized MRI was performed on a 3 Tesla MRI scanner (Magnetom Skyra, Siemens Healthineers, Erlangen, Germany) using flexible body coils. The MRI protocol includes a short tau inversion recovery sequence in the axial and coronal planes, a T2-weighted turbo spin echo (TSE) sequence in the axial plane, a T1-weighted TSE sequence in the coronal plane, a time-resolved MR angiography with the contrast agent gadobutrol (Gadovist©; Bayer, Leverkusen, Germany) and a T1-weighted high-resolution three-dimensional gradient echo with spectral fat saturation. The MRI datasets were reviewed by two independent radiologists with extensive experience in imaging of vascular anomalies.

Vascular malformation categorization

Assignment of malformation type was based on clinical diagnosis, which included evaluation of clinical examination, medical history records, and MRI scans of the legs and pelvis. Using the ISSVA classification, specific MRI features were assessed and patients were categorized into four cohorts: AVM, VM, LM and combined malformation (Table 1).[6] For combined vascular malformations, the genital malformation type was assessed separately from any malformations in extragenital regions of the pelvis and/or legs.

Magnetic resonance imaging assessment and correlation with clinical symptoms

To determine the prevalence of genital involvement in our study population, we used the MRI scans to assess the morphology of the external genitalia (female: labia majora and labia minora; male: penis and scrotum) and internal genitalia (female: vagina, uterus, ovary and cervix; male: testis, prostate and seminal vesicle). We also identified the distribution patterns and categorized the genital malformations into three groups: internal, external, or both external and internal (Fig. 1, lower half).

Table 1 Clinical diagnosis of genital involvement.

	Patients with:	
Clinical diagnosis[a]	Vascular malformation, *n*	Genital involvement, *n* (%)
All patients	370	71 (19.2)
Simple malformations		
Arteriovenous	61	6 (9.9)
Venous	167	22 (13.2)
Lymphatic	13	4 (30.8)
Combined malformations		
All	129	39 (30.2)
Capillary venous lymphatic	55	24 (43.6)
Venous lymphatic	20	6 (30.0)
Capillary venous	49	9 (18.4)
Capillary lymphatic	5	0 (0)

[a]Malformation types were verified by the patient's results (including medical history, clinical examination, magnetic resonance imaging).

To explore the prevalence of internal genital involvement in cases with external visible genital malformation signs, the medical records of patients with genital involvement in the MRI were accessed. We reviewed the clinical findings noted during the clinical examination and any associated genital symptoms. External involvement often produces visible symptoms such as soft tissue swelling, skin discoloration or dysplastic veins, and bleeding or lymphorrhoea.[2,3,6] These symptoms can often be noticed upon clinical examination and are described as 'visible malformation signs' for this study (see Fig. 2 as an example for visible malformation signs). Concomitant symptoms, such as pain and discomfort, as well as pregnancy-associated changes in symptoms, were also assessed. We correlated these clinical findings with the MRI findings to determine the prevalence of internal genital involvement in cases with visible signs on the external genitalia (Table 2).

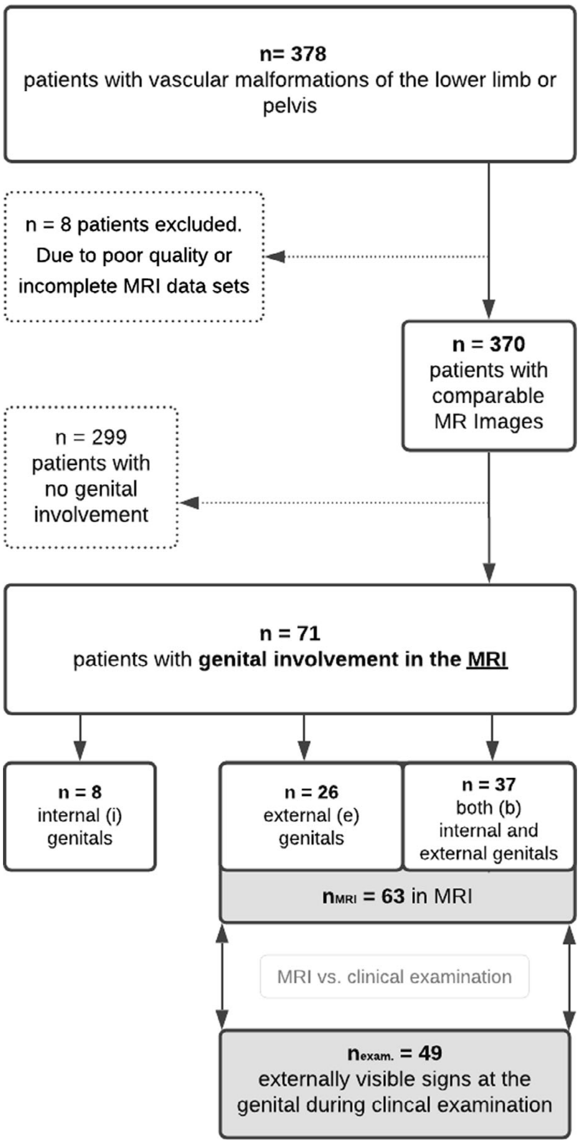

Figure 1 Subject flow diagram: inclusion and exclusion criteria are provided in the upper half, while the bottom half shows the differentiation of the patients into the three subcohorts, based on internal, external, or both external and internal genital involvement. MRI, magnetic resonance imaging.

Results

Magnetic resonance imaging scans

After analysing the MRIs of the 378 patients, 8 patients were excluded (5 had incomplete MRI acquisition, 3 had motion artefacts). Of the remaining 370 patients, 71 (19%) had signs of vascular malformations affecting the genitalia on their MRI scans (Fig. 1, upper half). Table 1 shows the different malformation types seen in the 370 patients and the percentages of participants with genital involvement for each malformation type. In our study population, we did not find any patients with simple capillary malformation, as this can usually be diagnosed without application of MRI.[17]

Categorization of vascular malformations

After identifying the 71 patients with genital involvement, the type of vascular malformation was verified by MRI (Table 2). In combined malformations, local genital findings can differ from those of other anatomical locations. For example, the capillary portion of a combined capillary VLM may involve only the distal leg, whereas the lymphatic and venous part of the malformation can be located in the genital area. This explains the apparent discrepancy in group sizes between Tables 1 and 2.

Correlation between results of clinical examination and magnetic resonance imaging

Table 2 provides the percentages of patients with internal, external, and both internal and external genital involvement as detected via MRI. Isolated internal involvement was detected in 8 patients (11%) and was most frequent in the AVM group; there were no cases in the VLM group. There were 26 patients (37%) with vascular malformation of the external genitals without involvement of internal genital structures, while 37

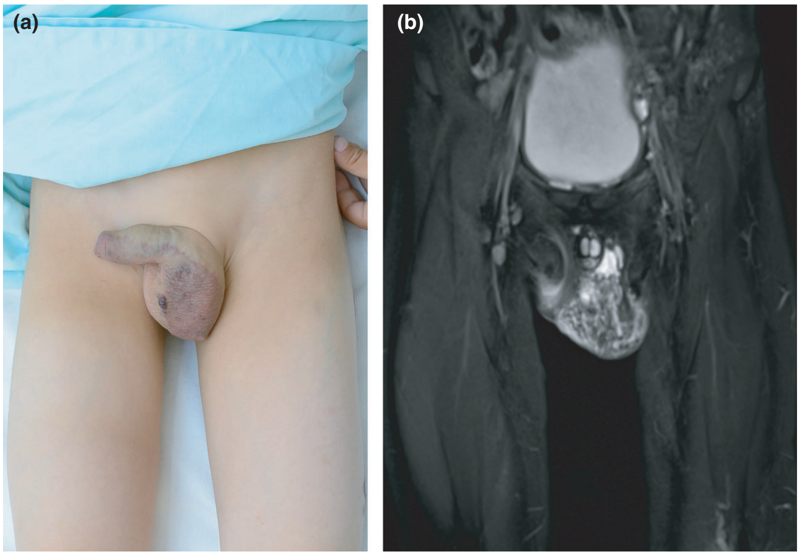

Figure 2 (a, b) Patient with capillary–venous–lymphatic malformation: (a) clinical image of the pelvis and thighs. (b) contrast-enhanced T1-weighted magnetic resonance image of the same area (coronal view), showing venous portions in scrotum and penis with prostate and seminal vesicle involvement, and capillary portions at the skin level of the scrotum and penis.

patients (52%) had involvement of both the external and internal genitalia.

Upon clinical examination (without the use of MRI), external genital involvement could be identified visually in 49 of the 71 patients (69%) noting symptoms such as bleeding, swelling, skin discoloration, dysplastic veins and lymphorrhoea (Table 2). By contrast, MRI scans assisted in the identification of 63 patients (total patient numbers for external and 'both' groups in Table 1 and bottom half of Fig. 1) with vascular malformation lesions on their external genitalia. Thus, even where there was external genital malformation, 22% of cases remained undetected by clinical examination (an example of a case with discrete external involvement and massive involvement of internal structures is shown in Fig. 3).

This discrepancy between clinical and MRI findings varied by sex, with 33 of female cases detected by clinical examination vs. 36 detected by MRI, compared with 16 vs. 27, respectively, for male cases.

Of the 49 patients who were found to have visible signs of malformation on the external genitalia during the clinical examination, 28 (57%) had additional internal genital involvement revealed by MRI. Distinct sex differences were observed for the occurrence of visible clinical signs on the external genitalia: the records of 33 of the 40 female patients (82.5%) and 16 of the 31 male patients (51.6%) described at least one of the predefined visible signs. Swelling and skin discoloration were found more often in female than in male patients (swelling: 60% vs. 22.6%; discoloration: 52.5% vs. 29%, respectively).

Of the 48 patients in the VM group (detected by MRI), 32 (67%) had external genital malformations that could be identified by means of clinical examination, with swelling being the most common sign, whereas 44 participants (92%) who had malformations identified by MRI also had external genital involvement that was seen on the MRI images (i.e. the MRI identified an additional 12 patients with external genital involvement that was missed by clinical examination). The proportion of patients with the lowest occurrence of externally visible signs was the AVM subgroup (16.7%). All patients in the VLM group and 87.5% in the LM group showed visible signs, with the most common findings being dysplastic veins (66.7%) and lymphorrhoea (62.5%), respectively.

Pain was the most pronounced concomitant symptom of malformations (45 of 71 patients, 63.4%). Another concomitant manifestation was worsening of symptoms such as swelling and bleeding during pregnancy, which was identified in five women in the VM group.

Discussion

In this study, we determined the prevalence of genital involvement in a relatively broad population of patients with vascular malformation of the legs and/or pelvic regions. Without considering malformation type or patient sex, 19% of the participants had malformation involvement in the external and/or internal genitalia. Vogel *et al.*, who investigated vascular anomalies in the external genitalia of female children, reported

Table 2 Magnetic resonance imaging and clinical findings.

Local malformation type	MRI findings Total (n = 71)[a]	Female (n = 40)	Male (n = 31)	Clinical findings and concomitant symptoms			
				Visible signs[b,c] (n = 49)		Pain (n = 45)[c]	
				Female (n = 33)	Male (n = 16)	Female (n = 30)	Male (n = 15)
AVM, n (%)	6 (8.5)	2 [5][d]	4 [13][d]	1	0	2	2
Internal	3		3				1
External	1	1		1		1	
Both	2	1	1			1	1
VM, n (%)	48 (67.6)	32 [80]	16 [52]	26	6	26	6
Internal	4	4				3	
External	19	13	6	12	2	11	1
Both	25	15	10	14	4	12	5
LM, n (%)	8 (11.3)	2 [5]	6 [19]	2	5		3
Internal	1		1				1
External	5	1	4	1	4		1
Both	2	1	1	1	1		1
VLM, n (%)	9 (12.7)	4 [10]	5 [16]	4	5	2	4
Internal							
External	1		1		1		1
Both	8	4	4	4	4	2	3

AVM, arteriovenous malformation; LM, lymphatic malformation; MRI, magnetic resonance imaging; VLM, venous lymphatic malformation; VM venous malformation. [a]MRI verified malformation types in patients with genital involvement (n = 71). [b]Visible signs during clinical examination were defined as swellings, bleeding, skin discolorations, dysplastic veins, lymphorrhoea or thrombophlebitis. [c]For each investigated malformation type, the total numbers of male and female patients with visually detected and painful genital malformations (results of clinical examination) are listed. [d]Values in square brackets indicate the relative frequency of gender-specific distributions.

that 1.9% (60 of 3186) of their participants had vascular malformation of the genitals.[8] This discrepancy between that study and ours may be explained by different inclusion criteria. The previous study included all types of vascular anomalies (vascular malformations and vascular tumours) and enrolled patients who displayed vascular anomalies anywhere in the body, not just the pelvis and/or legs.

The main objective of our study was to determine the probability that patients with a vascular malformation of the external genitalia detected using clinical findings such as swelling or skin discoloration would have additional internal genital involvement. Our findings indicated that 57% of patients (37 of 63) with externally visible malformation signs had additional internal genital involvement. A study from 2017

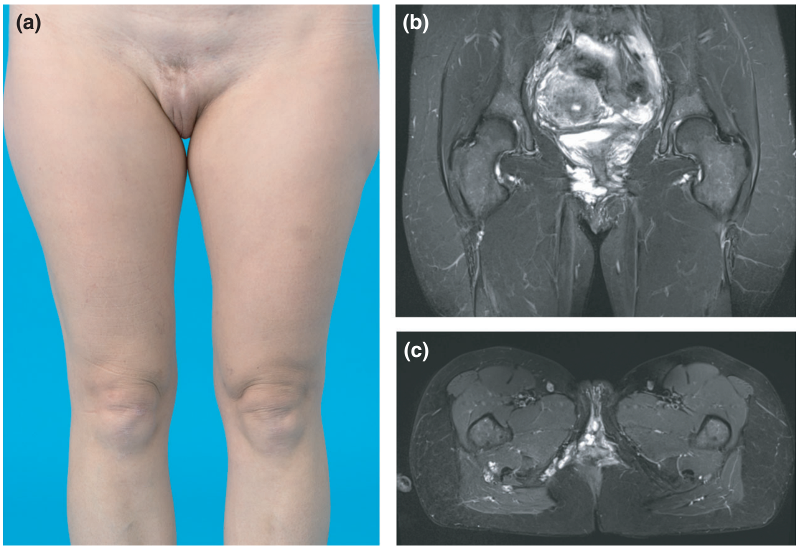

Figure 3 (a–c) Venous malformation: (a) clinical image of the pelvis and legs; (b,c) contrast-enhanced T1-weighted magnetic resonance image in (b) coronal view and (c) axial view of the same area, showing discrete external involvement of the right labia and extensive internal involvement (vagina, cervix, uterus, right ovary).

determined the frequency of an additional internal vascular anomaly in cases of focal genital venous malformations to be 45% (10 of 22 patients).[18] Despite different inclusion criteria regarding malformation types, our results confirm that approximately 50% of external genital cases also have internal involvement. This suggests that in cases of vascular malformation of the external genitalia, a small externally visible finding is often combined with a larger internal lesion, which can cause substantial health concerns if undetected.

The fact that external genital involvement was undetected in 22% of the cases by clinical examination supports the need for MRI in these cases. Possible reasons why some vascular malformation with external involvement were not identified during clinical examination may include patient reluctance to report local symptoms or a relatively deep malformation that involves the subcutaneous external genitalia and may not be sufficiently close to the skin to be noticeable.

Consequently, our findings confirm the importance of using additional imaging in the detection and treatment of vascular malformations. In these cases, MRI should be the technique of choice as it provides excellent soft-tissue contrast and high spatial resolution, and allows for tracking of flow patterns using a contrast agent with high specificity and sensitivity.[4,10,15,16,19]

In the current study, five patients with VM reported worsening of symptoms during pregnancy, which supports other studies that focused on female genitalia[3,9] and should be considered in the clinical care of women of childbearing age.

There are some limitations of our study that should be considered. First, we used a retrospective study design, which may result in less accurate patient reports compared with a prospective study. Another limitation is the heterogeneity of our study population. Other studies have focused on one entity such as VM or included only one sex.[3,9,18] Conversely, the heterogeneity of our study may also be a strength, as it may represent a more realistic patient population comparable to that seen in everyday clinical practice. It also enabled us to generate a relatively large sample size in this specific field compared with previous studies (which had 60,[7] 56,[8] 22[9] and 8[18] patients).

Conclusion

Our study showed a strong association between vascular malformation of the legs and/or pelvis and genitalia in both males and females. More importantly, we showed that additional involvement of internal genital structures is a common finding in patients with visible malformation lesions of the external genitalia. This highlights the importance of using MRI in malformation diagnostics as it increases the chance of identifying additional internal genital involvement. In several cases MRI also detected discrete, visually inconspicuous malformations of the external genitalia. Based on our findings, we recommend that whenever there is a suspicion of vascular malformation of the genital area or the legs, MRI of the pelvic region and legs should be performed at least once in the patient's lifetime.

What's already known about this topic?

- Vascular malformations can involve the genitalia in rare cases.
- Involvement of the external genitalia is mostly detectable via clinical examination, whereas internal genital involvement needs further diagnostic tools.
- MRI is the gold standard technique to understand the underlying pathology of the vessel architecture and flow characteristics.

What does this study add?

- Visible external genital involvement can be seen as tip of the iceberg, as around 50% of cases with visible vascular malformation signs at the external genitalia are also affected by additional internal genital involvement.
- MRI can detect cases with internal genital involvement even if there are no or only very subtle external signs.

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Erklärungen

(1) Ich erkläre, dass ich mich an keiner anderen Hochschule einem Promotionsverfahren unterzogen bzw. eine Promotion begonnen habe.

(2) Ich erkläre, die Angaben wahrheitsgemäß gemacht und die wissenschaftliche Arbeit an keiner anderen wissenschaftlichen Einrichtung zur Erlangung eines akademischen Grades eingereicht zu haben.

(3) Ich erkläre an Eides statt, dass ich die Arbeit selbstständig und ohne fremde Hilfe verfasst habe. Alle Regeln der guten wissenschaftlichen Praxis wurden eingehalten; es wurden keine anderen als die von mir angegebenen Quellen und Hilfsmittel benutzt und die den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht.

30.05.2022 *Constantin Immanuel Goldann*

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