厚生労働科学研究費補助金

難治性疾患等政策研究事業（難治性疾患政策研究事業）

# 難治性血管腫・血管奇形・リンパ管腫・リンパ管腫症および関連疾患 についての調査研究

（H29-難治等（難）-一般-０１４）

平成30年度　総括・分担研究報告書

研究代表者　秋田定伯

平成31（2019）年　3月

# 目　　次

厚生労働科学研究費補助金（難治性疾患等政策研究事業(難治性疾患政策研究事業)）
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# 難治性血管腫・血管奇形・リンパ管腫・リンパ管腫症および関連疾患についての調査研究

研究代表者　：　　秋田定伯（福岡大学医学部形成外科・創傷再生学講座　教授）

**研究要旨**：本研究は血管腫・血管奇形・リンパ管腫・リンパ管腫症およびその関連疾患を対象とする。これらの疾患には長期にわたり患者のQOLを深刻に損なう多くの難治性の病態が含まれる。これまでに平成21-23年度難治性血管腫・血管奇形研究班（佐々木班)、平成24-25年度　同研究班（三村班)、平成21-23年リンパ管腫研究班（藤野班)、平成24-25年度リンパ管腫症研究班（小関班)、平成24-25年度小児期からの消化器系希少難治性疾患研究班（田口班）の分担研究である腹部リンパ管腫研究、肝血管腫・血管奇形研究を発展させ、相互に協力して疾患概念の形成と疾患に対する啓発、普及及び患者診療に貢献することを目的とする。
脈管奇形（血管性及びリンパ管性）のうち、対象疾患が①静脈奇形、②動静脈奇形、③混合型脈管奇形（混合型血管奇形）、④リンパ管奇形（リンパ管腫）、⑤リンパ管腫症・ゴーハム病から、それぞれ①巨大静脈奇形（頚部口腔咽頭びまん性病変）、②巨大動静脈奇形（頚部顔面又は四肢病変）、③クリッペル・トレノネー・ウェーバー症候群、④巨大リンパ管奇形(頚部顔面病変)、⑤リンパ管腫症／ゴーハム病に変更となった。これらは指定難病に認定された。
診断基準、重症度分類は、乳幼児管巨大血管腫及び指定難病として関連学会の承認を受ける。
診療ガイドラインでは、佐々木班・三村班ではISSVA分類を発展し血管腫、血管奇形・リンパ管奇形・混合型奇形の調査研究内で、MINDS手法を用いて血管腫・血管奇形・リンパ管奇形診療ガイドライン策定・重症度分類・診断基準作成、疫学調査を行ってきた。三村班成果として、平成28年12月に改訂版完成し、日本形成外科学会・日本IVR学会、日本皮膚科学会・小児外科学会等の年度内に承認を受けている。
先天性リンパ管疾患には、同一異称や、混同病態の疾患があり、診断・治療も困難となっておりISSVA分類による脈管疾患のリンパ管奇形分類との整合性と小児慢性特定疾病と指定難病との整合性を図る必要もある。平成28年度までの藤野分担班ではリンパ管腫の全国調査が行われ、診断基準（案)、重症・難治性度診断基準（案）が作成された。小関分担班ではリンパ管腫症の全国調査が行われた。リンパ管腫及びリンパ管腫症は異なる病態を示すものの病理学的には鑑別出来ず、確定診断が困難な状態であったが、先の調査研究により全国調査がなされそれぞれの診断基準（案）が作成されるに到っている。
今後関連各学会、患者団体の意見を統合して提言し、広く医学会・社会の認知を得ることを目的とする。本年度は、現行の小児慢性疾病と指定難病の取り扱う疾病の整理と移行期（トランジショナル）医療への提案を脈管奇形について助言する。
研究の実施経過：血管腫・血管奇形・リンパ管奇形診療ガイドライン 2017 の完成と普及・啓発のための研究班ホームページの充実、横断的班員（分担研究者および研究協力者）構成、小児慢性特定疾病に新規疾病群として、脈管系疾患群および脈管奇形（青色ゴムまり様母班症候群、巨大静脈奇形、巨大動静脈奇形、クリッペル・トレノネー・ウェーバー症候群、原発性リンパ浮腫、リンパ管腫、リンパ管腫症）の創設に向けて提言した。また指定難病（リンパ管腫症・ゴーハム病（指定難病告示番号 277)、巨大リンパ管奇形（頚部顔面病変（指定難病告示番号 278)、巨大静脈奇形（頚部航空咽頭びまん性病変）(指定難病告示番号 279)、巨大動静脈奇形(頚部顔面又は四肢病変）(指定難病告示番号 280)、クリッペル・トレノネー・ウェーバー症候群(指定難病告示番号 281)、乳幼児肝巨大血管腫（指定難病告示番号 295）については、診断基準、重症度分類。診療ガイドライン、難病プラットフォーム(RADDAR-J)連携の“ レジストリ登録 ”における疾患、項目毎作成。ＥＰＣを完成した。患者会との合同シンポジウム（平成 30 年 7 月 20 日　第 15 回日本血管腫・血管奇形学会）および一般市民向け公開講座（平成 30 年 9 月 29 日、松本市）などで普及・啓発実施している。小児慢性特定疾病について医療補助申請案内ポスターを日本形成外科学会、日本 IVR 学会、日本血管腫・血管奇形学会にて解説説明した。

## A．研究目的

血管腫、血管奇形、リンパ管奇形、リンパ管腫症の普及啓発、診断基準の普及、重症度分類を周知し、診療ガイドラインの周知や、関連学術団体との交流、普及啓発を行い、更に当該患者会や社会一般市民向けに本分野の疾病概念の周知と医療補助、診療体制に繋がるレジストリ構築へ協力することを目的とする。

## B．研究方法

1. 診療ガイドラインの学会など専門科間での周知

平成 29 年 3 月完成の血管腫・血管奇形。リンパ管奇形診療ガイドラインのパブリックコメント収集と学会での承認依頼

2. 移行期（トランジショナル）医療としての小児慢性特定疾病への脈管奇形疾患群の政策提言

脈管奇形（血管奇形、リンパ管奇形）は平成 25 年三村班での全国調査でいずれの疾病も 10 歳台までの小児期に発症、治療開始となっており、現行の指定難病に繋がる疾患群の対応と早期の医療補助などの仕組みの提言を行政指導と助言のもと提言する

3. 普及啓発のための患者会との連携、市民公開講座開催

平成 30 年 7 月第 15 回日本血管腫・血管奇形学会〈大阪市〉での患者会参加型シンポジウム開催と平成 30 年 9 月 29 日福岡市での市民公開講座開催により患者会連携および社会啓発普及に努めた。

4. 難病プラットフォーム（RADDAR-J）基盤・連携下における本研究班担当疾患（血管奇形、指定難病 5 疾患及び小児慢性特定疾病 7 疾患）の“レジストリ”作成とバイオマーカー及び遺伝子探索プラットフォームの構築開始

**（倫理面への配慮）**

福岡大学【医に関する倫理委員会】で審査後、平成 29 年 11 月 1 日承認されている（整理番号 2016M096）

## C. 研究結果

1. 診療ガイドラインの周知　学会承認

平成 29 年 12 月までに、血管腫・血管奇形・リンパ管奇形診療ガイドラインの学会承認を日本形成外科学会、日本皮膚科学会、日本医放射線学会、日本小児科学会、日本 IVR 学会、日本病理学会、日本小児外科学会から得ており、ガイドラインに対するパブリックコメントも収集終了し MINDS 機構評価を受けた。

2. 小児慢性特定疾病の拡充に伴い脈管系疾患群の創設への助言と指定難病との連動

脈管奇形（青色ゴムまり様母班症候群、巨大静脈奇形、巨大動静脈奇形、クリッペル・トレノネー・ウェーバー症候群、原発性リンパ浮腫、リンパ管腫、リンパ管腫症）の創設となり、また指定難病（リンパ管腫症・ゴーハム病（指定難病告示番号 277)、巨大リンパ管奇形（頚部顔面病変（指定難病告示番号 278)、巨大静脈奇形（頚部航空咽頭びまん性病変）（指定難病告示番号 279)、巨大動静脈奇形（頚部顔面又は四肢病変）(指定難病告示番号 280)、クリッペル・トレノネー・ウェーバー症候群（指定難病告示番号 281）は、診断基準、重症度分類。診療ガイドライン、レジストリ登録　等　疾患、項目毎に再検討した。小児慢性特定疾病は指定難病に比較して、部位限定が少なく、より救済的な観点からの医療補助となった。

尚　本ポスターは日本形成外科学会認定施設、日本 IVR 学会認定施設、日本血管腫・血管奇形学会会員に承認のもと配布し、該当学会年次総会開催期間中のポスター配布及び関連学会講演で解説した。


3. 患者会との連携、市民公開講座

平成 30 年 7 月 20 日　大阪市での第 15 回日本血管腫・血管奇形学会内で　シンポジウム「患者 first に向けての取り組み」が開催され、研究班―患者会（三団体）―立法府との連携に取り組んだ。

平成 30 年 9 月 29 日　松本市にて、市民公開講座　難治性血管腫・血管奇形・リンパ管腫・リンパ管腫症および関連疾患についての調査研究～血管腫・血管奇形・脈管奇形を正しく知っていただくために～を研究班代表、分担班員の講演の基調講演に引き続き、患者会および出席者との間でタウンホールミィーティング形式で質疑応答で開催し、血管腫・血管奇形の患者会、混合型脈管奇形の会、血管奇形ネットワークの 3 団体の代表者の参加を含め 100 名超の聴衆と班会議の普及啓発し、更に、患者会とともに保存的治療法の一環として、クリッペル・トレノネー・ウェーバー症候群などの若年発症、全身性の重症化する傾向の強い疾患に対して、保険収載を目指す「臨床研究」等にむけた準備を関係諸機関、諸氏と開始することが合意形成された。

引き続き平成 31 年度にむけて臨床研究のための計画立案、実施における患者会の協力、許認可省庁

との交渉を継続する事が確認された。


## D．考察

診療ガイドラインの作成と普及により、疾患概要がつかみにくく、横断的専門分野にわたる脈管奇形（血管奇形、リンパ管奇形、リンパ管腫症、混合型）の基礎的教育、普及啓発の基盤は整いつつあるが、未だに診療体制としては、地域偏在や、情報の偏重などがあるため、難病医療支援ネットワークへの積極的参加の必要がある。また、臨床属性データを含む情報統合基盤（難病プラットフォーム）への参加により、難病のナショナルデータベース構築に発展知る可能性があるため、特に当研究班担当の脈管奇形疾患の中で重症度の高いものから、低いものまでの網羅的な情報基盤としても期待が持てる。
小児慢性特定疾病から指定難病への継ぎ目のない医療補助体制が整ったので、今後は主に治療側の各種専門家へ積極的に精度の普及と啓発を進めていく必要がある。本年度は日本形成外科学会、日本 IVR 学会、日本血管腫・血管奇形学会にポスター配布して周知を計り、各々の年次総会でポスター貼付と関連講演計画をたてた。

市民公開講座は継続的に行うと、患者さんおよび社会で問題となっている事項が明確化するため、本年度以降も継続予定である。

## E．結論

脈管奇形（血管奇形、リンパ管奇形、混合型　など）の診療ガイドラインの普及啓発と、診療体制の整備への提言、移行期医療を含めた小児期、早期からの治療体制の確立など今後の課題となるが、患者会、社会での問題点を研究班での検討提案事項としていく事も重要と思われた。研究班ホームページは情報発信とともに、双方向の媒体プラットフォームとして進化させていく予定である。

## F．健康危険情報

該当なし（分担研究者の一部の臨床研究において合併症を認めたものの、重篤な因果関係を認めるものはない）

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**H. 知的財産権の出願・取得状況　（予定を含む）**

該当なし

厚生労働科学研究費補助金（難治性疾患等政策研究事業(難治性疾患政策研究事業)）

平成 30 年度　分担研究報告書

# 難治性血管腫・血管奇形・リンパ管腫・リンパ管腫症および関連疾患についての調査研究

## 分担課題　「血管腫・血管奇形・リンパ管奇形診療ガイドライン 2017」の英訳原稿作成<br>研究班ホームページの管理・アップデート

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**研究要旨**

「血管腫・血管奇形・リンパ管奇形診療ガイドライン 2017」の英訳を英文雑誌に投稿するため、草稿を作成した。平成 29 年度まではガイドライン翻訳を行い、平成 30 年度はこれをガイドライン作成グループ担当者に送付し校正を依頼した。この校正文をさらに校正し、文献整理を行い、Introduction、Materials and Methods などを追加して英文草稿を作成した。平成 31 年度再度校正を行い、出版社と相談し、英文 3 学会誌同時掲載を目指す。研究班ホームページの管理アップデートを行う。

### A．研究目的

「血管腫・血管奇形・リンパ管奇形診療ガイドライン 2017」の英文雑誌投稿を行う。研究班ホームページの管理アップデートを行う。

### B．研究方法

平成 30 年 4 月から８月にかけて日本皮膚科学会誌「The Journal of Dermatology」、日本小児科学会誌「Pediatrics International」、日本医学放射線学会誌「Japanese Journal of Radiology」の編集委員会とコンタクトを取り、ガイドライン英文雑誌掲載の相談を行った。7 月に英訳文の著者校正をガイドライン作成グループメンバーに依頼し、平成 31 年 1 月までに校正文を入手した。平成 30 年 12 月から平成 31 年 3 月にかけて文献整理をし、Introduction、Materials and Methods などを追加して英文草稿を作成した。研究班ホームページの管理アップデートを行った。

### C．研究結果

ガイドライン英文投稿原稿の草稿を作成した。平成３０年度時点での英文草稿を資料として添付する（資料１）。

研究班ホームページでは「血管腫・血管奇形・リンパ管奇形診療ガイドライン 2017」を掲載している。市民公開講座「血管腫・血管奇形・脈管奇形を正しく知って頂くために」「小児リンパ管疾患シンポジウム」、「血管腫血管奇形学会学術集会」の広報を行った。

### D．考察

血管腫・脈管奇形の疾患全体の診療ガイドラインは日本発のガイドライン「血管腫・血管奇形診療ガイドライン 2013」およびその改訂版「血管腫・血管奇形・リンパ管奇形診療ガイドライン 2017」があるのみで、他に国際的なガイドラインはみられない。今回「血管腫・血管奇形・リンパ管奇形診療ガイドライン 2017」の英訳を作成し、3 つの英文誌に同時掲載し、広報することを意図している。日本発の画期的なガイドラインとなると期待される。

さらに 3 誌はそれぞれ学会誌であり、国内においても多様な読者に広報することにより、さらに周知が図られるものと期待される。

研究班ホームページでは最新の情報をアップデートし、医療従事者、患者、市民への広報に努めた。

### E．結論

「血管腫・血管奇形・リンパ管奇形診療ガイドライン 2017」の英文投稿原稿の草稿を作成した。平成 31 年度再度校正を行い、出版社と相談し英文 3 学会誌同時掲載を目指す。

研究班ホームページでは最新の情報をアップデートした。

### F．研究発表

１．論文発表

（発表誌名巻号・頁・発行年等も記入）

1) Hashimoto K, Uchida B, Horikawa M, Mimura H, Farsad K. Effects of Different Mixing Agents on the Stability of Sodium Tetradecyl Sulfate (STS) Foam: An Experimental Study. Cardiovasc Intervent Radiol. 2018;41(12):1952-1957.

2) 三村秀文.硬化療法・塞栓術の実際. 大原國章, 神人正寿, 血管腫・血管奇形臨床アトラス, 南江堂, 東京, 2018:40-47.

3) 三村秀文.vascular anomalies(脈管異常). 画像診断増刊号 2018;38:76-81.

2．学会発表

1) Hidefumi Mimura. Vasc malformation general, Seminar for Interventional Radiology in Asia-Pacific 2018, Oct 2018.

2）Kazuki Hashimoto, Masahiro Horikawa, Barry Uchida, Khashayar Farsad, Hidefumi Mimura.The Durability of Sodium Tetradecyl Suphate (STS) Foam in vitro Model, 第 47 回日本 IVR 学会, May 2018.

3）三村秀文.血管奇形の IVR, 第 77 回日本医学放射線学会総会, 2018 年 4 月.

G．知的所有権の出願・取得状況（予定を含む

1 特許取得

なし

2 実用新案登録

なし

3 その他

なし

厚生労働科学研究費補助金（難治性疾患等政策研究事業）
分担研究報告書

# 2199例の臨床データに基づく静脈奇形の疼痛発生率の解析

研究分担者　力久直昭　千葉労災病院形成外科部長

**研究要旨**
**Type of Research:　多施設間，レトロスペクティブ，横断的な 研究.**
**Key Findings: 四肢体幹の筋骨腱に達する静脈奇形の疼痛発生率は79％、四肢体幹/皮膚皮下までの病変では43％、頭頸部/筋骨腱では28％、頭頸部/皮膚皮下では11％であり、それぞれで有意差を認めた（p ＜ 0.01）。病変大きさ別の発生率は直径10ｃｍ以上で67％、　5ｃｍ以上10ｃｍ未満で56％、5ｃｍ未満で29％であり、有意差を認めた（p ＜ 0.01）。四肢体幹の病変では年齢増加に伴い疼痛合併例が増加し、7歳を超えると発生率が50％を超えた。**
**Take Home Message: 静脈奇形の疼痛に関与する因子は部位　深さ　大きさ　年齢の順であり、それぞれ四肢体幹の病変　筋骨に達する病変　5㎝以上の病変　7歳以上の患者で疼痛を合併しやすいことがわかった。**

## A．研究目的

**静脈奇形の主な症状は、腫脹　疼痛　感染　潰瘍出血などである。特に疼痛は通学や就労を妨げるためQOLを著しく下げてしまう。頭頚部の静脈奇形は下肢病変に比べて疼痛の頻度が少ないことが経験上知られている。疼痛を伴いやすい静脈奇形の特徴について調べた。**

## B．研究方法

**調査項目**

患者の性別　初診時の年齢
病変の部位（頭頚部と四肢体幹に分けて集計）
病変の深達度（「皮膚皮下まで」と「筋骨腱に達する」に分けて集計）
病変の大きさ（最大径が5㎝未満　5㎝以上10㎝未満　10㎝以上の3つグループに分けて集計）

**調査対象**

平成25年に行った血管腫血管奇形の全国疫学調査で集められた患者データ（85施設から回答があり、VM患者は2199例）から解析を行った。

**解析方法**

それぞれの項目について集計表を作りカイ二乗検定を行った。さらに各項目が持つ疼痛発生への寄与度を解析するため多変量解析の一種である二項ロジスティク解析を行った。

## C．研究結果（平成30年度）

| | 頭頚部 | 四肢体幹 |
|---|---|---|
| **疼痛発生率** | **20%*** | **63%*** |
| **合計数** | *878* | *1265* |
| **男性／女性** | *334 / 544* | *481 / 784* |
| **平均年齢** | *31 歳* | *24 歳* |
| **年齢中央値** | *27 歳* | *20 歳* |

**疼痛発生率は頭頚部で20%、四肢体幹で63%だった。それぞれの男女比や初診時の年齢は表のようになり有意差はなかった。**

| 部位 | 深さ | 疼痛発生率 | *疼痛なし* | *疼痛あり* |
|---|---|---|---|---|
| 頭頸部 | 皮膚皮下 | **11%*** | *388* | *50* |
| | 筋骨腱 | **28%*** | *298* | *116* |
| 四肢体幹 | 皮膚皮下 | **43%*** | *308* | *230* |
| | 筋骨腱 | **79%*** | *144* | *541* |

**病変の深達度でみると、膚皮下までの浅い病変は筋骨腱に達する深い病変のたいして疼痛発生率が小さいことがわかった。頭頚部の皮膚皮下病変の疼痛発生率は11%　筋骨腱では28%　四肢体幹では皮膚皮下病変の疼痛発生率は43%　筋骨腱では79%でそれぞれに有意差があった。**

| 深さ | | 疼痛発生率 | *疼痛なし* | *疼痛あり* |
|---|---|---|---|---|
| 下記合計 | 男性 | **42%** | *471* | *345* |
| | 女性 | **47%** | *703* | *626* |
| 皮膚皮下 | 男性 | *15%* | *283* | *51* |
| | 女性 | *23%* | *421* | *123* |
| 筋骨腱 | 男性 | *61%* | *188* | *294* |
| | 女性 | *64%* | *282* | *503* |

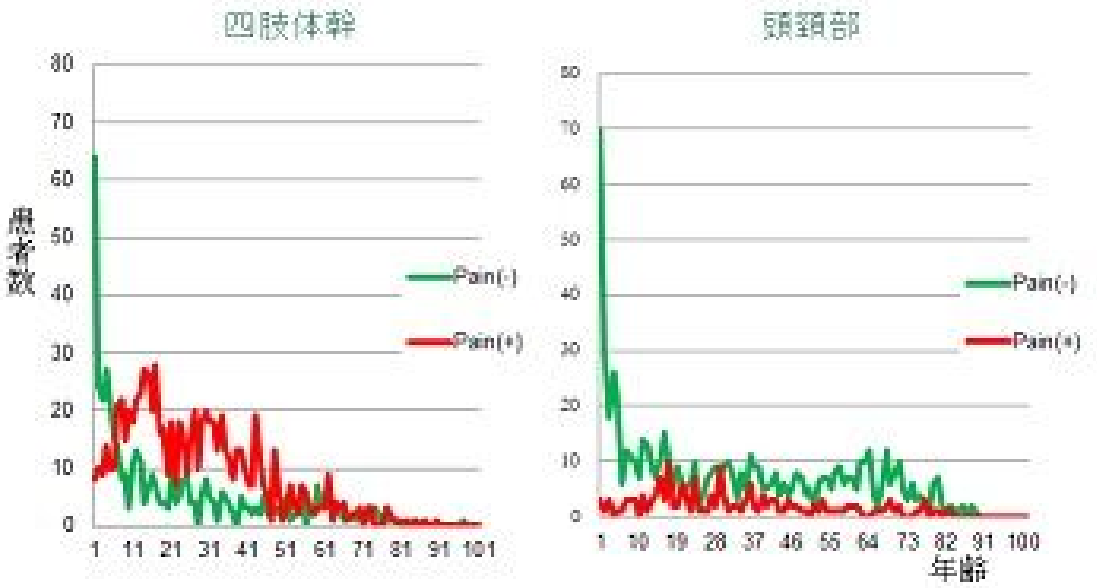
**性別による有意差はみられなかった。念のため病変の深さ別に男女差がないかも確認した。**

| 最大径 | 疼痛発生率 | *疼痛なし* | *疼痛あり* |
|---|---|---|---|
| ５㎝以下 | **29%*** | *716* | *290* |
| ５～１０㎝ | **56%*** | *237* | *274* |
| １０㎝以上 | **67%*** | *185* | *373* |

**病変が大きいほど疼痛の頻度が上昇することがわかった。**

| 独立変数 | 偏回帰係数 | 標準誤差 | 標準偏回帰係数 | P値 | 95%信頼区間偏回帰係数 | オッズ比 | 95%信頼区間オッズ比 |
|---|---|---|---|---|---|---|---|
| 年齢 | 0.0124 | 0.0025 | 0.2732 | **0.0000** | 0.0075 to 0.0172 | **1.0124** | 1.0076 to 1.0173 |
| 性別 | 0.2027 | 0.1077 | 0.0985 | 0.0597 | -0.0083 to 0.4138 | 1.2247 | 0.9117 to 1.5125 |
| 部位 | 2.0553 | 0.1179 | 1.0108 | **0.0000** | 1.8242 to 2.2864 | **7.8092** | 6.1977 to 9.8397 |
| 深さ | 1.2303 | 0.1151 | 0.6140 | **0.0000** | 1.0047 to 1.4559 | **3.4224** | 2.7312 to 4.2885 |
| 大きさ | 0.4014 | 0.0677 | 0.3374 | **0.0000** | 0.2687 to 0.5341 | **1.4939** | 1.3082 to 1.7059 |
| 定数項 | -2.9424 | 0.1664 | | **0.0000** | -3.2686 to -2.6162 | **0.0527** | 0.0381 to 0.0731 |

二項ロジスティック解析の結果を示す。オッズ比が大きいほど寄与度高いといえる。病変の部位のオッズ比が一番高くなった。年齢と病変の大きさの間に交絡関係はなかった。また上記二項ロジスティック解析で求まる計算式によって疼痛合併を予想した場合、その的中率は75%であった。




初診時年齢と疼痛の関係を示すグラフ

左上のグラフは四肢体幹の症例では疼痛を示す赤い線が6－7歳で緑色を超える。四肢体幹の症例は小学生になるころから半数以上で疼痛が発生している。

右上のグラフは頭頚部の症例を示す。疼痛を伴なわない症例を示す緑の線が加齢とともに下がっていく。15歳くらいで疼痛ありの症例とほぼ同じ数になることもあるが、疼痛を合併する赤い線が緑を超えることはない。

D．考察

静脈奇形の疼痛に関与する因子は、部位　深さ　大きさ　年齢の順であり、四肢体幹の病変　筋骨に達する病変　5cm以上の病変　7歳以上の患者で疼痛を合併しやすいことがわかった。各施設で症例を検討した際に、上記の疼痛発生率を超えるようであれば治療ストラテジーの再考を要し、逆に大幅に下回るのであれば、有効な治療をおこなっているといえる。

静脈奇形の疼痛発生機序について詳細は不明であり、local intravascular coagulopathyの関与が高いとされている。今後は血液データの蓄積が望まれ、これにより疼痛発生予防につながるかもしれない。

E．結論

静脈奇形の疼痛に関与する因子は、部位　深さ　大きさ　年齢の順であり、四肢体幹の病変　筋骨に達する病変　5cm以上の病変　7歳以上の患者で疼痛を合併しやすいことがわかった。

F．健康危険情報

静脈奇形の疼痛に関与する因子は、部位　深さ　大きさ　年齢の順であり、四肢体幹の病変　筋骨に達する病変　5cm以上の病変　7歳以上の患者で疼痛を合併しやすい。

G．研究発表

1．　論文発表

Jourenal of Vasucular Surgery in press

2．　学会発表

2019年5月　日本形成外科総会（札幌）発表予定

H．知的財産権の出願・登録状況

出願予定なし

厚生労働科学研究費補助金（難治性疾患等政策研究事業(難治性疾患政策研究事業)）

分担研究報告書

# 難治性血管腫・血管奇形・リンパ管腫・リンパ管腫症および関連疾患についての調査研究

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研究要旨：脈管奇形疾患群の一つである巨大動静脈奇形は、進行性の先天性疾患のため、小児期より発症し医療機関で通院加療を要する場合が多い。、本年度小児慢性特定疾病に組み入れられた巨大動静脈奇形について、小児期に発症した指定難病としての巨大動静脈奇形（頸部顔面又は四肢）との照合により、小児期・成人期移行医療の整備を検討した。

## A．研究目的

脈管奇形疾患群の一つとして、本年度、小児慢性特定疾病に採択された巨大動静脈奇形について、診断の手引きを確認し、今後の小児期・成人期移行医療の整備を検討した。

## B．研究方法

小児慢性特定疾病における診断基準について確認を行い、指定難病との診断基準との照合を行った。

## C．研究結果

小児慢性特定疾病における巨大動静脈奇形の診断基準は以下の通りである。

大分類：脈管奇形

細分類：巨大動静脈奇形

状態の程度：疾病による症状がある場合又は治療が必要な場合

＜診断基準＞

a. 症状：血管の拡張や蛇行が見られ、拍動やスリルを触知し、血管雑音を聴取する。

b. 検査所見：

b-1. 超音波、MRI 、CT、動脈造影などの画像診断で、動静脈の異常な拡張や吻合を認め、病変内に動脈血流を有する。

b-2.　病理検査で、動脈と静脈の中間的な構造を示す種々の径の血管が不規則に集簇している。

b-3. 病変が患者の手掌大(※)以上の大きさである。（※患者本人の指先から手関節までの手掌の面積）

c. 遺伝学的検査：本疾患に特異的な遺伝子検査は現時点で行われていない。

d. 鑑別診断：

d-1.血管を構成する細胞の腫瘍性疾患（乳児血管腫、血管肉腫など）

d-2.後天性の血管病変（一次性静脈瘤、二次性リンパ浮腫、外傷性・医原性動静脈瘻、動脈瘤など）

「確実例」a, b-1 または b-2、かつ b3 の項目を満たし、d の鑑別疾患を除外できる。

「疑い例」a の項目のみ認める。

## D．考察

巨大動静脈奇形は、先天性かつ進行性の高流速型の脈管奇形であり、小児期に発症し、医療機関の通院・加療が必要な場合が多く、小児慢性特定疾病への採択は有意義である。指定難病との照合においては、必ずしも小児期には重症度が高くない患者が、成人移行期にかけて重症へと進行する可能性があることや、指定難病で規定されない頸部顔面・四肢以外の患者の扱いなどが今度の課題となる。

## E．結論

小児慢性特定疾病に採択された巨大動静脈奇形に関して、今後は小児期に発症した指定難病である巨大動静脈奇形（頸部顔面又は四肢）との照合を踏まえて、小児期・成人期移行医療の整備が望まれる。

## F．研究発表

論文発表

欧文

1. Kimura Y, Osuga K, Ono Y, Nakazawa T, Higashihara H,

Tomiyama N. Long-term outcomes of selective renal artery embolization for renal arteriovenous fistulae with dilated venous sac. J Vasc Interv Radiol. 29(7):952-7, 2018

**和文**

1. **大須賀慶悟：**Arteriovenous malformations (AVM:**動静脈奇形**)**．血管腫・血管奇形臨床アトラス．大原國章，神人正寿編．南江堂，東京**2018, pp123-5.

## G．知的所有権の出願・取得状況（予定を含む

1　**特許取得**

　　**なし**

2　**実用新案登録**

　　**なし**

3　**その他**

　　**なし**

厚生労働科学研究費補助金　難治性疾患等政策研究事業(難治性疾患克政策研究事業)
「難治性血管腫・血管奇形・リンパ管種・リンパ管種症および関連疾患についての調査研究」
平成 30 年度　研究報告書

# 診療報酬記録からみた血管腫・血管奇形・リンパ管腫・リンパ管腫症関連疾患の全国推定患者数の算出の試み（2014–2016）

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（広島大学　大学院医系科学研究科　疫学・疾病制御学　助教）

**研究要旨**

難治性血管腫・血管奇形のうち、末梢性同静脈奇形、クリッペル・トレノネー症候群、クリッペル・トレノーネイ・ウェーバ症候群・リンパ管腫・リンパ管腫症関連疾患の患者数を、健康保険組合に加入している本人および家族の全診療報酬記録（以下レセプト）のデータから推計することを試みた。全国の健康保険組合 1,500 組合, 対象数 3,000 万人のうち日本医療データセンター（JMDC）が保有する全国に出張所がある 52 の事業所に所属する本人、及び家族（0 歳-74 歳）の 3,460,784 人が有する診療報酬記録 77,793,046 件を対象とした。65 歳以上の対象が少ないため、64 歳以下の 3,362,460 人を解析対象とした。

上記対象レセプトから、標準病名に母斑、血管腫、リンパ管腫、静脈奇形、動静脈奇形、血管奇形、先天性動静脈瘻、スタージ・ウェーバ症候群、クリッペル・トレノネー症候群、クリッペル・トレノーネイ・ウェーバ症候群を含む含むレセプトを抽出した。

抽出したレセプトを対象に、さらに詳しい標準病名をもとに、内臓血管腫を除外し、疾患の部位が特定できるもの「部位特定可」、特定できないもの「部位特定不可」に分類した。患者数を 1 年ごとに、性・年齢階級別に集計して 1 年期間有病率を算出した。算出した 1 年期間有病率をもとに 0-64 歳の日本人口 92,175,546 人における患者数を推計した。

・[2014 年]  血管腫関連患者数　　118,662 人(95%CI:106,139-131,187)
　　うちリンパ管腫　　6,566 人(95%CI:3,509-9,665)
・[2015 年]  血管腫関連患者数　　126,247 人(95%CI:113,509-138,986)
　　うちリンパ管腫　　7,133 人(95%CI:3,955-10,326)
・[2016 年]  血管腫関連患者数　　132,330 人(95%CI:119,187-145,472)
　　うちリンパ管腫　　6,956 人(95%CI:3,841-10,095)

指定難病の要件では患者数が人口の 0.1%程度以下であるとされている。本研究の 2015 年の血管腫関連患者数は人口の 0.13%と推定され、指定難病の要件の患者数と同程度であることが示唆された。

## A 研究目的

患者数の把握が困難な希少疾患である難治性血管腫・血管奇形のうち、末梢性同静脈奇形、クリッペル・トレノネー症候群、クリッペル・トレノーネイ・ウェーバ症候群・リンパ管腫・リンパ管腫症関連疾患の患者数を、健康保険組合に加入している本

人および家族の全診療報酬記録のデータから推計することを試みた。

## B 研究方法

### 1) 解析対象

健康保険組合は全国約 1,500 あり、その対象者数は約 3,000 万人である。そのうち、52 の健康保険組合に属する本人および家族（0–74 歳）の 2014–2016 年の全診療報酬記録を対象とした。

対象数は 3,460,784 人が有する診療報酬記録 7,793,046 件である。解析対象の 2015 年における性・年齢階級別対象者数を図１（左）に示す。65 歳以上の対象が少ないため、64 歳以下の 3,362,460 人を解析対象とした。

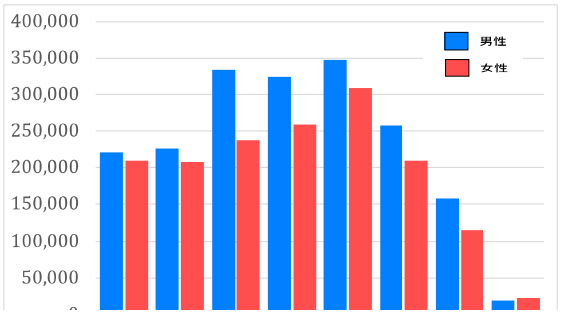


図１全対象集団 3,460,784 人の性・年齢階級分布

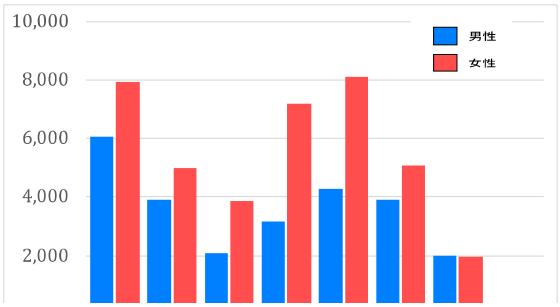


図 2 血管腫関連病名レセプトを持つ 65,081 人の性・年齢階級分布

### 2)解析方法

対象レセプトから標準病名に「母斑」、「血管腫」、「リンパ管腫」、「静脈奇形」、「動静脈奇形」、「血管奇形」、「先天性動静脈瘻」、「スタージ・ウェーバ症候群」、「クリッペル・トレノネー症候群」、「クリッペル・トレノーネイ・ウェーバ症候群」を含むものを抽出した。抽出したレセプトを対象に、さらに詳しい標準病名をもとに、疾患の部位が特定できるもの「部位特定可」（別表１）、特定できないもの「部位特定不可」（別表２）に分類した。抽出された患者数は 65,081 人であった。65,801 人の性･年齢階級別分布を図２に示す。

なお、消化管以外の内臓病変、中枢神経病変の病名（別表３）のみを持つ 55,381 人を除外した。

2014 年と 2016 年に同じ標準病名のレセプトを持ち、間の 2015 年にレセプトがない場合は、2015 年にもその標準病名を持つと仮定した。部位特定可と部位特定不可の病名両方を持っている患者は部位特定可として集計した。

抽出したレセプトを個人識別 ID・診療年月でソートし、性・年齢階級別・疾患別に集計して１年期間有病率を算出した。算出した１年期間有病率と 0-64 歳人口から全国推定患者数を算出した。集計フローチャートを図３に示す。

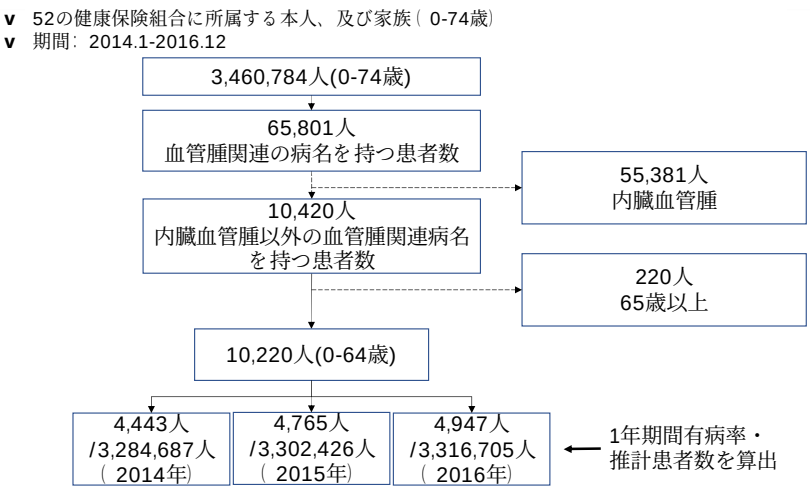


図３集計フローチャート

C **結果**

2014-2016 年における 0-64 歳の血管腫関連 1 年期間有病率、及びリンパ管腫 1 年期間有病率(10 万人対)を表 1 に示す。

血管腫関連の 1 年期間有病率は 2014 年：135.0（95%CI:131.0-138.9)、2015 年：144.3（95%CI:140.2-148.4)、2016 年：149.2(95%CI:145.0-153.3)であった。

うちリンパ管腫の 10 万人対の 1 年期間有病率は 2014 年：7.2（95%CI:6.4-8.2)、2015 年：8.0（95%CI:7.1-9.0)、2016 年：7.7(95%CI:6.8-8.7)であった。

**表 1　0-64 歳の血管腫関連疾患の 1 年期間有病率　10 万人対**

| | 全体 95%CI | 部位特定可 95%CI | 部位特定不可 95%CI |
|---|---|---|---|
| 2014 | | | |
| 血管腫関連有病率 | 135.0 (131.0-138.9) | 63.5 (60.8-66.2) | 71.4 (68.5-74.3) |
| うちリンパ管腫有病率 | 7.2 (6.4-8.2) | | |
| 2015 | | | |
| 血管腫関連有病率 | 144.3 (140.2-148.4) | 70.8 (68.0-73.7) | 73.4 (70.5-76.4) |
| うちリンパ管腫有病率 | 8.0 (7.1-9.0) | | |
| 2016 | | | |
| 血管腫関連有病率 | 149.2 (145.0-153.3) | 73.8 (70.9-76.7) | 75.4 (72.4-78.3) |
| うちリンパ管腫有病率 | 7.7 (6.8-8.7) | | |

算出した 0-64 歳の 1 年期間有病率をもとに 0-64 歳人口 92.175,546 人における患者数を推計した。推計患者数を表 2 に示す。

血管腫関連患者数は

2014 年：118,662 人(95%CI:106,139-131,187)、2015 年：126,247 人(95%CI:113,509-138,986)、2016 年：132,330人(95%CI:119,187-145,472)であった。

うちリンパ管腫は

2015 年：6,566 人(95%CI:3,509-9,665)、

2015 年：7,133 人(95%CI:3,955-10,326)、

2016 年：6,956 人(95%CI:3,841-10,095)であった。

**表 2　0-64 歳日本人口 92,175,546 人における血管腫関連疾患推計患者数**

| | 全体 95%CI | 部位特定可 95%CI | 部位特定不可 95%CI |
|---|---|---|---|
| 2014 | | | |
| 患者数 | 118,662 (106,139-131,187) | 55,148 (46,748-63,548) | 63,515 (54,256-72,773) |
| うちリンパ管腫 | 6,566 (3,509-9,665) | | |
| 2015 | | | |
| 患者数 | 126,247 (113,509-138,986) | 61,805 (52,973-70,636) | 64,415 (55,252-73,579) |
| うちリンパ管腫 | 7,133 (3,955-10,326) | | |
| 2016 | | | |
| 患者数 | 132,330 (119,187-145,472) | 65,225 (56,047-74,403) | 67,104 (57,718-76,490) |
| うちリンパ管腫 | 6,956 (3,841-10,095) | | |

算出した血管腫関連疾患推計患者数を性別・年齢階級別に図 4 及び表 3 に示す。2014-2016 年いずれにおいても、0-9 歳の患者が最も多く、女性の患者数が多かった。

また、同様にリンパ管腫の推計患者数を性別・年齢階級別に図 5 及び表 4 に示す。リンパ管腫関連疾患においても 0-9 歳の患者が最も多かったが、0-9 歳階級においては女性より男性の患者数が多かった。

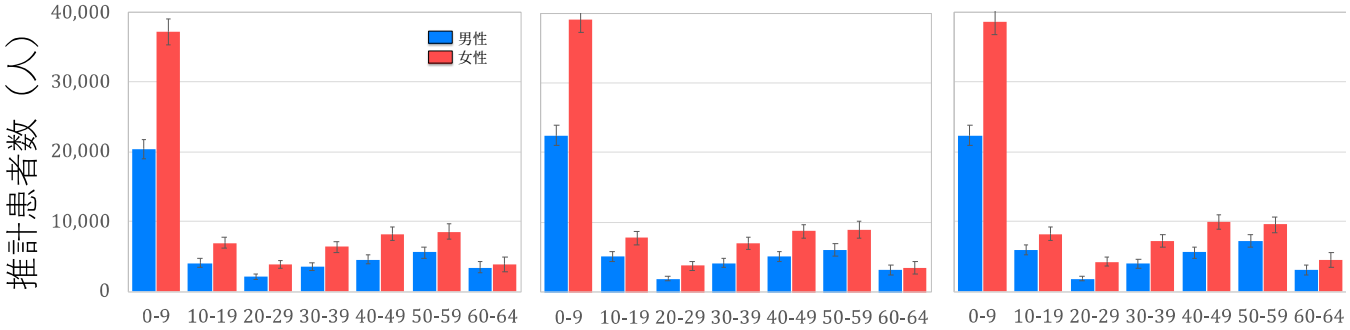


図 4　日本人口 92,175,546 人における血管腫関連疾患推計患者数
（左）2014 年、（中）2015 年、（右）2016 年

表 3　日本人口 92,175,546 人における性・年齢階級別血管腫関連疾患推計患者数

| 2014 年 | 男女 (95%CI) | 男性 (95%CI) | 女性 (95%CI) |
|---|---|---|---|
| 0-9 | 57,659 (54,455-61,341) | 20,424 (19,062-21,787) | 37,234 (35,393-39,076) |
| 10-19 | 11,035 (9,580-12,714) | 4,060 (3,445-4,676) | 6,975 (6,136-7,815) |
| 20-29 | 6,016 (5,011-7,243) | 2,141 (1,750-2,532) | 3,875 (3,261-4,488) |
| 30-39 | 9,844 (8,439-11,516) | 3,471 (2,902-4,039) | 6,373 (5,537-7,210) |
| 40-49 | 12,762 (11,085-14,728) | 4,562 (3,868-5,255) | 8,200 (7,217-9,183) |
| 50-59 | 14,087 (12,124-16,373) | 5,550 (4,731-6,370) | 8,537 (7,393-9,680) |
| 60-64 | 7,260 (5,444-9,298) | 3,403 (2,606-4,200) | 3,857 (2,838-4,876) |
| 合計 | 118,663 (106,139-131,187) | 43,611 (38,363-48,860) | 75,051 (67,776-82,327) |
| 2015 年 | 男女 (95%CI) | 男性 (95%CI) | 女性 (95%CI) |
| 0-9 | 61,489 (58,182-65,252) | 22,442 (21,015-23,868) | 39,048 (37,166-40,929) |
| 10-19 | 12,768 (11,179-14,546) | 5,067 (4,367-5,768) | 7,701 (6,812-8,590) |
| 20-29 | 5,616 (4,643-6,823) | 1,895 (1,526-2,265) | 3,721 (3,117-4,324) |
| 30-39 | 11,198 (9,686-12,972) | 4,168 (3,543-4,792) | 7,030 (6,143-7,917) |
| 40-49 | 13,761 (12,025-15,772) | 5,078 (4,348-5,807) | 8,683 (7,677-9,689) |
| 50-59 | 14,888 (12,919-17,157) | 5,991 (5,157-6,825) | 8,897 (7,762-10,031) |
| 60-64 | 6,527 (4,874-8,368) | 3,107 (2,374-3,840) | 3,421 (2,500-4,341) |
| 合計 | 126,247 (113,509-138,986) | 47,748 (42,331-53,165) | 78,500 (71,178-85,821) |
| 2016 年 | 男女 (95%CI) | 男性 (95%CI) | 女性 (95%CI) |
| 0-9 | 61,065 (57,759-64,824) | 22,362 (20,935-23,788) | 38,703 (36,823-40,583) |
| 10-19 | 14,166 (12,468-16,017) | 5,927 (5,154-6,699) | 8,239 (7,314-9,165) |
| 20-29 | 6,051 (5,044-7,340) | 1,813 (1,450-2,175) | 4,238 (3,594-4,883) |
| 30-39 | 11,199 (9,681-13,015) | 3,971 (3,361-4,580) | 7,228 (6,320-8,136) |
| 40-49 | 15,469 (13,655-17,588) | 5,551 (4,797-6,305) | 9,917 (8,858-10,977) |
| 50-59 | 16,771 (14,697-19,100) | 7,203 (6,294-8,112) | 9,568 (8,403-10,732) |
| 60-64 | 7,610 (5,884-9,648) | 3,106 (2,399-3,814) | 4,504 (3,485-5,522) |
| 合計 | 132,330 (119,187-145,472) | 49,932 (44,391-55,474) | 82,397 (74,796-89,999) |

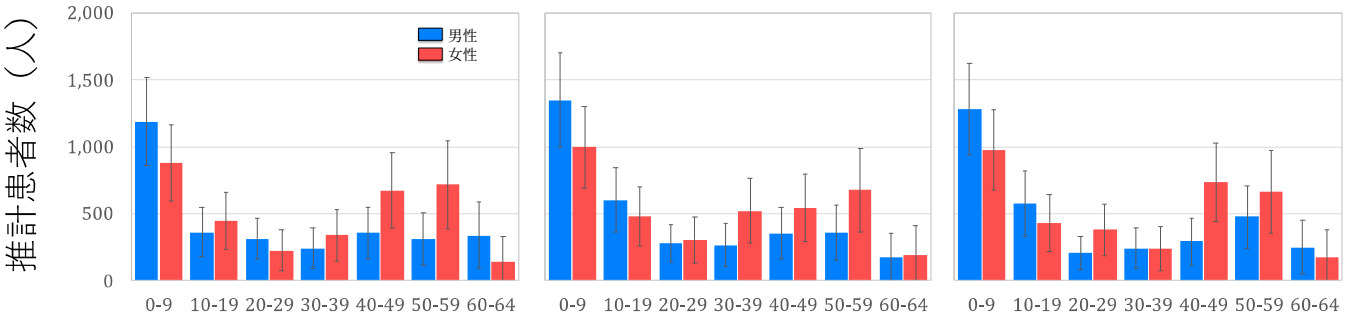


**図 5　日本人口 92,175,546 人におけるリンパ管腫関連疾患推計患者数**
**（左）2014 年、（中）2015 年、（右）2016 年**

**表 4　日本人口 92,175,546 人における性・年齢階級別リンパ管腫関連疾患推計患者数**

| 2014 年 | 男女 (95%CI) | 男性 (95%CI) | 女性 (95%CI) |
|---|---|---|---|
| 0-9 | 2,071 (1,457-2,641) | 1,187 (858-1,517) | 884 (599-1,168) |
| 10-19 | 812 (415-1,238) | 365 (180-549) | 447 (235-660) |
| 20-29 | 544 (245-842) | 317 (166-467) | 228 (79-377) |
| 30-39 | 586 (241-974) | 243 (92-393) | 343 (149-537) |
| 40-49 | 1,033 (556-1,598) | 357 (163-551) | 676 (393-958) |
| 50-59 | 1,033 (506-1,697) | 315 (120-511) | 718 (386-1,050) |
| 60-64 | 481 (88-869) | 340 (88-592) | 140 (0-335) |
| 合計 | 6,560 (3,509-9,665) | 3,124 (1,668-4,581) | 3,436 (1,841-5,085) |
| 2015 年 | 男女 (95%CI) | 男性 (95%CI) | 女性 (95%CI) |
| 0-9 | 2,350 (1,697-2,954) | 1,351 (1,000-1,701) | 999 (697-1,301) |
| 10-19 | 1,086 (622-1,531) | 605 (363-847) | 481 (259-704) |
| 20-29 | 587 (272-933) | 281 (139-424) | 306 (133-479) |
| 30-39 | 793 (392-1,278) | 268 (110-427) | 525 (283-768) |
| 40-49 | 901 (456-1,406) | 355 (162-548) | 546 (294-799) |
| 50-59 | 1,042 (523-1,669) | 363 (158-569) | 679 (365-992) |
| 60-64 | 374 (4-812) | 180 (4-357) | 194 (0-413) |
| 合計 | 7,133 (3,965-10,326) | 3,403 (1,935-4,872) | 3,730 (2,030-5,455) |
| 2016 年 | 男女 (95%CI) | 男性 (95%CI) | 女性 (95%CI) |
| 0-9 | 2,267 (1,623-2,868) | 1,285 (942-1,627) | 982 (681-1,282) |
| 10-19 | 1,011 (557-1,436) | 577 (336-818) | 434 (221-646) |
| 20-29 | 591 (274-978) | 208 (85-330) | 383 (189-577) |
| 30-39 | 482 (166-811) | 244 (93-395) | 238 (73-403) |
| 40-49 | 1,031 (569-1,610) | 294 (120-467) | 738 (449-1,027) |
| 50-59 | 1,143 (602-1,757) | 478 (244-713) | 665 (358-972) |
| 60-64 | 432 (50-840) | 252 (50-453) | 180 (0-384) |
| 合計 | 6,956 (3,841-10,095) | 3,336 (1,870-4,803) | 3,620 (1,971-5,291) |

D **まとめ**

**難治性血管腫・血管奇形疾患関連患者数**を、**健康保険組合**に**加入**している**本人**および**家族**の**全診療報酬記録**のデータから**推計した**。**全国**の**健康保険組合** 1,500 **組合**, **対象数** 3,000 **万人**のうち**日本医療データセンター**（JMDC）**が保有**する**全国**に**出張所**がある 52 **の事業所**に**所属**する**本人**、**及**び**家族**（0 **歳**-74 **歳**）の 3,460,784 **人**からなる**診療報酬記録** 77,793,046 **件**を**対象**とした。65 **歳以上**の**対象**が**少**ないため、64 **歳以下**の 3,362,460 **人**を**解析対象**とした。

**患者数**を 1 **年**ごとに、**性・年齢階級別**に**集計**して 1 **年期間有病率**を**算出**した。**算出**した 1 **年期間有病率**を**もとに** 0-64 **歳**の**日本人口** 92,175,546 **人**における**患者数**を**推計**した。

**血管腫関連患者数**は
2014 **年**：118,662 **人**(95%CI:106,139-131,187)、2015 **年**：126,247 **人**(95%CI:113,509-138,986)、2016 **年**：132,330 **人**(95%CI:119,187-145,472)**であった**。

**うちリンパ管腫**は
2015 **年**：6,566 **人**(95%CI:3,509-9,665)、
2015 **年**：7,133 **人**(95%CI:3,955-10,326)、
2016 **年**：6,956 **人**(95%CI:3,841-10,095)**であった**。

**指定難病**の**要件**では**患者数**が**人口**の 0.1%**程度以下**であるとされている。**本研究**の 2015 **年**の**血管腫関連患者数**は**人口**の 0.13%**と推定**され、**指定難病**の**要件**の**患者数と同程度**であることが**示唆**された。

E **研究発表**

**該当**なし

F **健康危険情報**

**該当**なし

G **知的財産権**の**出現・登録状況**

**該当**なし

## 別表１　「部位特定可」：集計対象とする標準病名、標準病名から部位が特定できるもの(1/2)

| ICD10小分類 | ICD10細分類 | 標準病名 |
|---|---|---|
| D18(血管腫及びリンパ管腫，全ての部位) | D180(血管腫，全ての部位) | 下咽頭血管腫 |
| | D180(血管腫，全ての部位) | 咽頭血管腫 |
| | D180(血管腫，全ての部位) | 陰のう血管腫 |
| | D180(血管腫，全ての部位) | 陰茎海綿状血管腫 |
| | D180(血管腫，全ての部位) | 下口唇血管腫 |
| | D180(血管腫，全ての部位) | 下腿血管腫 |
| | D180(血管腫，全ての部位) | 外陰部血管腫 |
| | D180(血管腫，全ての部位) | 環指血管腫 |
| | D180(血管腫，全ての部位) | 眼瞼血管腫 |
| | D180(血管腫，全ての部位) | 眼窩内血管腫 |
| | D180(血管腫，全ての部位) | 顔面血管腫 |
| | D180(血管腫，全ての部位) | 頚部血管腫 |
| | D180(血管腫，全ての部位) | 肩部血管腫 |
| | D180(血管腫，全ての部位) | 口唇血管腫 |
| | D180(血管腫，全ての部位) | 喉頭血管腫 |
| | D180(血管腫，全ての部位) | 甲状腺血管腫 |
| | D180(血管腫，全ての部位) | 項部血管腫 |
| | D180(血管腫，全ての部位) | 腰部血管腫 |
| | D180(血管腫，全ての部位) | 示指血管腫 |
| | D180(血管腫，全ての部位) | 耳下腺血管腫 |
| | D180(血管腫，全ての部位) | 手掌血管腫 |
| | D180(血管腫，全ての部位) | 手背血管腫 |
| | D180(血管腫，全ての部位) | 手部血管腫 |
| | D180(血管腫，全ての部位) | 十二指腸血管腫 |
| | D180(血管腫，全ての部位) | 小指血管腫 |
| | D180(血管腫，全ての部位) | 上眼瞼血管腫 |
| | D180(血管腫，全ての部位) | 上口唇血管腫 |
| | D180(血管腫，全ての部位) | 上腕血管腫 |
| | D180(血管腫，全ての部位) | 舌海綿状血管腫 |
| | D180(血管腫，全ての部位) | 舌血管腫 |
| | D180(血管腫，全ての部位) | 前胸部血管腫 |
| | D180(血管腫，全ての部位) | 前腕血管腫 |
| | D180(血管腫，全ての部位) | 足底血管腫 |
| | D180(血管腫，全ての部位) | 足部血管腫 |
| | D180(血管腫，全ての部位) | 体幹血管腫 |
| | D180(血管腫，全ての部位) | 大腿血管腫 |
| | D180(血管腫，全ての部位) | 中指血管腫 |
| | D180(血管腫，全ての部位) | 殿部血管腫 |
| | D180(血管腫，全ての部位) | 乳腺血管腫 |
| | D180(血管腫，全ての部位) | 背部血管腫 |
| | D180(血管腫，全ての部位) | 腹部血管腫 |
| | D180(血管腫，全ての部位) | 母指血管腫 |
| | D180(血管腫，全ての部位) | 頬粘膜血管腫 |
| | D180(血管腫，全ての部位) | 頬部血管腫 |
| | D180(血管腫，全ての部位) | 腋窩血管腫 |
| | D181(リンパ管腫，全ての部位) | 頚部のう胞性リンパ管腫 |
| | D181(リンパ管腫，全ての部位) | 前胸部リンパ管腫 |
| | D181(リンパ管腫，全ての部位) | 足関節部のう胞性リンパ管腫 |
| | D181(リンパ管腫，全ての部位) | 大腿リンパ管腫 |
| | D181(リンパ管腫，全ての部位) | 背部リンパ管腫 |
| | D181(リンパ管腫，全ての部位) | 肘関節部のう胞性リンパ管腫 |
| | D181(リンパ管腫，全ての部位) | 肘関節部リンパ管腫 |

## 別表１　「部位特定可」：集計対象とする標準病名、標準病名から部位が特定できるもの(2/2)

| ICD10小分類 | ICD10細分類 | 標準病名 |
|---|---|---|
| D23(皮膚のその他の良性新生物) | D235(皮膚のその他の良性新生物，体幹の皮膚) | 母斑様限局性体幹被角血管腫 |
| D29(男性生殖器の良性新生物) | D294(男性生殖器の良性新生物，陰のう<嚢>) | 陰のう被角血管腫 |
| D36(その他の部位及び部位不明の良性新生物) | D360(その他の部位及び部位不明の良性新生物，リンパ | 腋窩リンパ管腫 |
| E75(スフィンゴリピド代謝障害及びその他の脂質蓄積障害) | E752(その他のスフィンゴリピドーシス) | びまん性体幹被角血管腫 |
| Q27(末梢血管系のその他の先天奇形) | Q273(末梢性動静脈奇形) | 巨大動静脈奇形（四肢病変） |
| | Q278(末梢血管系のその他の明示された先天奇形) | 巨大静脈奇形（頚部口腔咽頭びまん性病変） |
| Q82(皮膚のその他の先天奇形) | Q825(先天性非腫瘍<非新生物>性母斑) | ウンナ母斑 |
| | Q825(先天性非腫瘍<非新生物>性母斑) | 下肢単純性血管腫 |
| | Q825(先天性非腫瘍<非新生物>性母斑) | 下腿部単純性血管腫 |
| | Q825(先天性非腫瘍<非新生物>性母斑) | 顔面いちご状血管腫 |
| | Q825(先天性非腫瘍<非新生物>性母斑) | 顔面単純性血管腫 |
| | Q825(先天性非腫瘍<非新生物>性母斑) | 胸部いちご状血管腫 |
| | Q825(先天性非腫瘍<非新生物>性母斑) | 胸部単純性血管腫 |
| | Q825(先天性非腫瘍<非新生物>性母斑) | 手部単純性血管腫 |
| | Q825(先天性非腫瘍<非新生物>性母斑) | 上肢単純性血管腫 |
| | Q825(先天性非腫瘍<非新生物>性母斑) | 上腕部単純性血管腫 |
| | Q825(先天性非腫瘍<非新生物>性母斑) | 正中部母斑 |
| | Q825(先天性非腫瘍<非新生物>性母斑) | 前腕部単純性血管腫 |
| | Q825(先天性非腫瘍<非新生物>性母斑) | 大腿部単純性血管腫 |
| | Q825(先天性非腫瘍<非新生物>性母斑) | 背部単純性血管腫 |
| | Q825(先天性非腫瘍<非新生物>性母斑) | 腹部単純性血管腫 |
| | Q825(先天性非腫瘍<非新生物>性母斑) | 頬部単純性血管腫 |
| Q85(母斑症，他に分類されないもの) | Q858(その他の母斑症，他に分類されないもの) | スタージ・ウェーバ症候群 |

**別表２　「部位特定不可」：集計対象とする標準病名、標準病名から部位が特定できないもの(2/2)**

| ICD10小分類 | ICD10細分類 | 標準病名 |
|---|---|---|
| D18(血管腫及びリンパ管腫，全ての部位) | D180(血管腫，全ての部位) | つる状血管腫 |
| | D180(血管腫，全ての部位) | 海綿状血管腫 |
| | D180(血管腫，全ての部位) | 筋肉内血管腫 |
| | D180(血管腫，全ての部位) | 血管腫 |
| | D180(血管腫，全ての部位) | 静脈性血管腫 |
| | D180(血管腫，全ての部位) | 多発性海綿状血管腫 |
| | D180(血管腫，全ての部位) | 毛細血管性血管腫 |
| | D180(血管腫，全ての部位) | 幼児性血管腫 |
| | D181(リンパ管腫，全ての部位) | のう胞性リンパ管腫 |
| | D181(リンパ管腫，全ての部位) | リンパ管腫 |
| | D181(リンパ管腫，全ての部位) | 血管リンパ管腫 |
| | D181(リンパ管腫，全ての部位) | 膝窩部のう胞性リンパ管腫 |
| D36(その他の部位及び部位不明の良性新生物) | D369(その他の部位及び部位不明の良性新生物，部位不明の良性新生物) | 被角血管腫 |
| | D369(その他の部位及び部位不明の良性新生物，部位不明の良性新生物) | ミベリ被角血管腫 |
| | D369(その他の部位及び部位不明の良性新生物，部位不明の良性新生物) | 単発性被角血管腫 |
| L81(その他の色素異常症) | L817(色素性紫斑性皮膚症) | 蛇行状血管腫 |
| M89(その他の骨障害) | M895(骨溶解（症）) | リンパ管腫症 |
| Q27(末梢血管系のその他の先天奇形) | Q273(末梢性動静脈奇形) | 先天性動静脈瘤 |
| | Q273(末梢性動静脈奇形) | 先天性動静脈瘻 |
| | Q273(末梢性動静脈奇形) | 末梢性動静脈奇形 |
| | Q279(末梢血管系の先天奇形，詳細不明) | ＡＶＭ |
| | Q279(末梢血管系の先天奇形，詳細不明) | 末梢血管奇形 |
| Q82(皮膚のその他の先天奇形) | Q825(先天性非腫瘍<非新生物>性母斑) | いちご状血管腫 |
| | Q825(先天性非腫瘍<非新生物>性母斑) | 血管性母斑 |
| | Q825(先天性非腫瘍<非新生物>性母斑) | 単純性血管腫 |
| | Q828(皮膚のその他の明示された先天奇形) | 血管腫症 |
| | Q828(皮膚のその他の明示された先天奇形) | 青色ゴムまり様母斑症候群 |
| Q87(多系統に及ぶその他の明示された先天奇形症候群) | Q872(先天奇形症候群，主として(四)肢の障害されたもの) | クリッペル・トレノーネイ・ウェーバ症候群 |
| | Q872(先天奇形症候群，主として(四)肢の障害されたもの) | クリッペル・トレノネー症候群 |

## 別表３　「除外」：集計対象から除外する標準病名（消化管以外の内臓病変、中枢神経病変は除外する）(1/4)

| ICD10小分類 | ICD10細分類 | 標準病名 |
|---|---|---|
| C43(皮膚の悪性黒色腫) | C439(皮膚の悪性黒色腫，部位不明) | 異形成母斑症候群 |
| D18(血管腫及びリンパ管腫，全ての部位) | D180(血管腫，全ての部位) | 胃血管腫 |
| | D180(血管腫，全ての部位) | 肝海綿状血管腫 |
| | D180(血管腫，全ての部位) | 肝血管腫 |
| | D180(血管腫，全ての部位) | 肝硬化性血管腫 |
| | D180(血管腫，全ての部位) | 眼底血管腫 |
| | D180(血管腫，全ての部位) | 結膜血管腫 |
| | D180(血管腫，全ての部位) | 食道血管腫 |
| | D180(血管腫，全ての部位) | 腎血管腫 |
| | D180(血管腫，全ての部位) | 脊髄血管腫 |
| | D180(血管腫，全ての部位) | 脊椎血管腫 |
| | D180(血管腫，全ての部位) | 大腸血管腫 |
| | D180(血管腫，全ての部位) | 頭蓋内血管腫 |
| | D180(血管腫，全ての部位) | 頭部血管腫 |
| | D180(血管腫，全ての部位) | 脳血管腫 |
| | D180(血管腫，全ての部位) | 肺血管腫 |
| | D180(血管腫，全ての部位) | 肺硬化性血管腫 |
| | D180(血管腫，全ての部位) | 脈絡膜血管腫 |
| | D180(血管腫，全ての部位) | 網膜血管腫 |
| | D180(血管腫，全ての部位) | 脾血管腫 |
| | D180(血管腫，全ての部位) | 膀胱血管腫 |
| | D180(血管腫，全ての部位) | 膵血管腫 |
| | D181(リンパ管腫，全ての部位) | 腹腔内リンパ管腫 |
| D22(メラニン細胞性母斑) | D220(口唇のメラニン細胞性母斑) | 下口唇青色母斑 |
| | D220(口唇のメラニン細胞性母斑) | 下口唇母斑 |
| | D220(口唇のメラニン細胞性母斑) | 下口唇母斑細胞母斑 |
| | D220(口唇のメラニン細胞性母斑) | 下口唇扁平母斑 |
| | D220(口唇のメラニン細胞性母斑) | 口唇母斑細胞母斑 |
| | D220(口唇のメラニン細胞性母斑) | 上口唇青色母斑 |
| | D220(口唇のメラニン細胞性母斑) | 上口唇母斑 |
| | D220(口唇のメラニン細胞性母斑) | 上口唇母斑細胞母斑 |
| | D220(口唇のメラニン細胞性母斑) | 上口唇扁平母斑 |
| | D221(眼瞼のメラニン細胞性母斑，眼角を含む) | 下眼瞼青色母斑 |
| | D221(眼瞼のメラニン細胞性母斑，眼角を含む) | 下眼瞼母斑 |
| | D221(眼瞼のメラニン細胞性母斑，眼角を含む) | 下眼瞼母斑細胞母斑 |
| | D221(眼瞼のメラニン細胞性母斑，眼角を含む) | 下眼瞼扁平母斑 |
| | D221(眼瞼のメラニン細胞性母斑，眼角を含む) | 眼瞼青色母斑 |
| | D221(眼瞼のメラニン細胞性母斑，眼角を含む) | 眼瞼母斑 |
| | D221(眼瞼のメラニン細胞性母斑，眼角を含む) | 眼瞼母斑細胞母斑 |
| | D221(眼瞼のメラニン細胞性母斑，眼角を含む) | 上眼瞼母斑 |
| | D221(眼瞼のメラニン細胞性母斑，眼角を含む) | 上眼瞼母斑細胞母斑 |
| | D221(眼瞼のメラニン細胞性母斑，眼角を含む) | 上眼瞼扁平母斑 |
| | D222(耳及び外耳道のメラニン細胞性母斑) | 耳介母斑細胞母斑 |
| | D222(耳及び外耳道のメラニン細胞性母斑) | 耳母斑細胞母斑 |
| | D223(その他及び部位不明の顔面のメラニン細胞性母斑) | 顔面脂腺母斑 |
| | D223(その他及び部位不明の顔面のメラニン細胞性母斑) | 顔面青色母斑 |
| | D223(その他及び部位不明の顔面のメラニン細胞性母斑) | 顔面母斑 |
| | D223(その他及び部位不明の顔面のメラニン細胞性母斑) | 顔面母斑細胞母斑 |
| | D223(その他及び部位不明の顔面のメラニン細胞性母斑) | 顔面扁平母斑 |
| | D223(その他及び部位不明の顔面のメラニン細胞性母斑) | 前額部青色母斑 |
| | D223(その他及び部位不明の顔面のメラニン細胞性母斑) | 前額部母斑 |
| | D223(その他及び部位不明の顔面のメラニン細胞性母斑) | 前額部母斑細胞母斑 |
| | D223(その他及び部位不明の顔面のメラニン細胞性母斑) | 前額部扁平母斑 |
| | D223(その他及び部位不明の顔面のメラニン細胞性母斑) | 側頭部青色母斑 |
| | D223(その他及び部位不明の顔面のメラニン細胞性母斑) | 太田母斑 |
| | D223(その他及び部位不明の顔面のメラニン細胞性母斑) | 鼻部青色母斑 |
| | D223(その他及び部位不明の顔面のメラニン細胞性母斑) | 鼻部母斑 |
| | D223(その他及び部位不明の顔面のメラニン細胞性母斑) | 鼻部母斑細胞母斑 |
| | D223(その他及び部位不明の顔面のメラニン細胞性母斑) | 鼻部扁平母斑 |
| | D223(その他及び部位不明の顔面のメラニン細胞性母斑) | 頬部青色母斑 |
| | D223(その他及び部位不明の顔面のメラニン細胞性母斑) | 頬部母斑 |
| | D223(その他及び部位不明の顔面のメラニン細胞性母斑) | 頬部母斑細胞母斑 |
| | D223(その他及び部位不明の顔面のメラニン細胞性母斑) | 頬部扁平母斑 |

**別表３　「除外」：集計対象から除外する標準病名（消化管以外の内臓病変、中枢神経病変は除外する）** (2/4)

| ICD10小分類 | ICD10細分類 | 標準病名 |
|---|---|---|
| D22(メラニン細胞性母斑) | D224(頭皮及び頚部のメラニン細胞性母斑) | 頚部青色母斑 |
| | D224(頭皮及び頚部のメラニン細胞性母斑) | 頚部母斑 |
| | D224(頭皮及び頚部のメラニン細胞性母斑) | 頚部母斑細胞母斑 |
| | D224(頭皮及び頚部のメラニン細胞性母斑) | 頚部扁平母斑 |
| | D224(頭皮及び頚部のメラニン細胞性母斑) | 側頭部母斑 |
| | D224(頭皮及び頚部のメラニン細胞性母斑) | 側頭部母斑細胞母斑 |
| | D224(頭皮及び頚部のメラニン細胞性母斑) | 頭皮青色母斑 |
| | D224(頭皮及び頚部のメラニン細胞性母斑) | 頭皮母斑 |
| | D224(頭皮及び頚部のメラニン細胞性母斑) | 頭皮母斑細胞母斑 |
| | D224(頭皮及び頚部のメラニン細胞性母斑) | 頭皮扁平母斑 |
| | D224(頭皮及び頚部のメラニン細胞性母斑) | 頭部脂腺母斑 |
| | D225(体幹のメラニン細胞性母斑) | ベッカー母斑 |
| | D225(体幹のメラニン細胞性母斑) | 胸部青色母斑 |
| | D225(体幹のメラニン細胞性母斑) | 胸部母斑 |
| | D225(体幹のメラニン細胞性母斑) | 胸部母斑細胞母斑 |
| | D225(体幹のメラニン細胞性母斑) | 胸部扁平母斑 |
| | D225(体幹のメラニン細胞性母斑) | 体幹青色母斑 |
| | D225(体幹のメラニン細胞性母斑) | 体幹母斑 |
| | D225(体幹のメラニン細胞性母斑) | 体幹母斑細胞母斑 |
| | D225(体幹のメラニン細胞性母斑) | 体幹扁平母斑 |
| | D225(体幹のメラニン細胞性母斑) | 殿部青色母斑 |
| | D225(体幹のメラニン細胞性母斑) | 殿部母斑 |
| | D225(体幹のメラニン細胞性母斑) | 殿部母斑細胞母斑 |
| | D225(体幹のメラニン細胞性母斑) | 殿部扁平母斑 |
| | D225(体幹のメラニン細胞性母斑) | 背部青色母斑 |
| | D225(体幹のメラニン細胞性母斑) | 背部母斑 |
| | D225(体幹のメラニン細胞性母斑) | 背部母斑細胞母斑 |
| | D225(体幹のメラニン細胞性母斑) | 背部扁平母斑 |
| | D225(体幹のメラニン細胞性母斑) | 腹部青色母斑 |
| | D225(体幹のメラニン細胞性母斑) | 腹部母斑 |
| | D225(体幹のメラニン細胞性母斑) | 腹部母斑細胞母斑 |
| | D225(体幹のメラニン細胞性母斑) | 腹部扁平母斑 |
| | D226(上肢のメラニン細胞性母斑，肩を含む) | 伊藤母斑 |
| | D226(上肢のメラニン細胞性母斑，肩を含む) | 環指母斑細胞母斑 |
| | D226(上肢のメラニン細胞性母斑，肩を含む) | 肩青色母斑 |
| | D226(上肢のメラニン細胞性母斑，肩を含む) | 肩母斑 |
| | D226(上肢のメラニン細胞性母斑，肩を含む) | 肩母斑細胞母斑 |
| | D226(上肢のメラニン細胞性母斑，肩を含む) | 肩扁平母斑 |
| | D226(上肢のメラニン細胞性母斑，肩を含む) | 示指母斑細胞母斑 |
| | D226(上肢のメラニン細胞性母斑，肩を含む) | 手青色母斑 |
| | D226(上肢のメラニン細胞性母斑，肩を含む) | 手母斑 |
| | D226(上肢のメラニン細胞性母斑，肩を含む) | 手母斑細胞母斑 |
| | D226(上肢のメラニン細胞性母斑，肩を含む) | 手扁平母斑 |
| | D226(上肢のメラニン細胞性母斑，肩を含む) | 小指母斑細胞母斑 |
| | D226(上肢のメラニン細胞性母斑，肩を含む) | 上腕青色母斑 |
| | D226(上肢のメラニン細胞性母斑，肩を含む) | 上腕母斑 |
| | D226(上肢のメラニン細胞性母斑，肩を含む) | 上腕母斑細胞母斑 |
| | D226(上肢のメラニン細胞性母斑，肩を含む) | 上腕扁平母斑 |
| | D226(上肢のメラニン細胞性母斑，肩を含む) | 前腕青色母斑 |
| | D226(上肢のメラニン細胞性母斑，肩を含む) | 前腕母斑 |
| | D226(上肢のメラニン細胞性母斑，肩を含む) | 前腕母斑細胞母斑 |
| | D226(上肢のメラニン細胞性母斑，肩を含む) | 前腕扁平母斑 |
| | D226(上肢のメラニン細胞性母斑，肩を含む) | 中指母斑細胞母斑 |
| | D226(上肢のメラニン細胞性母斑，肩を含む) | 爪甲線状母斑 |
| | D226(上肢のメラニン細胞性母斑，肩を含む) | 母指母斑細胞母斑 |

## 別表３　「除外」：集計対象から除外する標準病名（消化管以外の内臓病変、中枢神経病変は除外する）(3/4)

| ICD10小分類 | ICD10細分類 | 標準病名 |
|---|---|---|
| D22(メラニン細胞性母斑) | D227(下肢のメラニン細胞性母斑，股関節部を含む) | 下腿青色母斑 |
| | D227(下肢のメラニン細胞性母斑，股関節部を含む) | 下腿母斑 |
| | D227(下肢のメラニン細胞性母斑，股関節部を含む) | 下腿母斑細胞母斑 |
| | D227(下肢のメラニン細胞性母斑，股関節部を含む) | 下腿扁平母斑 |
| | D227(下肢のメラニン細胞性母斑，股関節部を含む) | 足青色母斑 |
| | D227(下肢のメラニン細胞性母斑，股関節部を含む) | 足母斑 |
| | D227(下肢のメラニン細胞性母斑，股関節部を含む) | 足母斑細胞母斑 |
| | D227(下肢のメラニン細胞性母斑，股関節部を含む) | 足扁平母斑 |
| | D227(下肢のメラニン細胞性母斑，股関節部を含む) | 足蹠青色母斑 |
| | D227(下肢のメラニン細胞性母斑，股関節部を含む) | 足蹠母斑 |
| | D227(下肢のメラニン細胞性母斑，股関節部を含む) | 足蹠母斑細胞母斑 |
| | D227(下肢のメラニン細胞性母斑，股関節部を含む) | 大腿青色母斑 |
| | D227(下肢のメラニン細胞性母斑，股関節部を含む) | 大腿母斑 |
| | D227(下肢のメラニン細胞性母斑，股関節部を含む) | 大腿母斑細胞母斑 |
| | D227(下肢のメラニン細胞性母斑，股関節部を含む) | 大腿扁平母斑 |
| | D227(下肢のメラニン細胞性母斑，股関節部を含む) | 第２趾母斑細胞母斑 |
| | D227(下肢のメラニン細胞性母斑，股関節部を含む) | 第３趾母斑細胞母斑 |
| | D227(下肢のメラニン細胞性母斑，股関節部を含む) | 第４趾母斑細胞母斑 |
| | D227(下肢のメラニン細胞性母斑，股関節部を含む) | 第５趾母斑細胞母斑 |
| | D227(下肢のメラニン細胞性母斑，股関節部を含む) | 母趾母斑細胞母斑 |
| | D227(下肢のメラニン細胞性母斑，股関節部を含む) | 趾爪甲線状母斑 |
| | D229(メラニン細胞性母斑，部位不明) | サットン母斑 |
| | D229(メラニン細胞性母斑，部位不明) | 異形成母斑 |
| | D229(メラニン細胞性母斑，部位不明) | 境界母斑 |
| | D229(メラニン細胞性母斑，部位不明) | 脂腺母斑 |
| | D229(メラニン細胞性母斑，部位不明) | 真皮内母斑 |
| | D229(メラニン細胞性母斑，部位不明) | 青色母斑 |
| | D229(メラニン細胞性母斑，部位不明) | 点状集簇性母斑 |
| | D229(メラニン細胞性母斑，部位不明) | 複合母斑 |
| | D229(メラニン細胞性母斑，部位不明) | 母斑 |
| | D229(メラニン細胞性母斑，部位不明) | 母斑細胞母斑 |
| | D229(メラニン細胞性母斑，部位不明) | 毛包母斑 |
| | D229(メラニン細胞性母斑，部位不明) | 有毛性母斑細胞母斑 |
| | D229(メラニン細胞性母斑，部位不明) | 扁平母斑 |
| | D229(メラニン細胞性母斑，部位不明) | 疣状色素性母斑 |
| D23(皮膚のその他の良性新生物) | D239(皮膚のその他の良性新生物，皮膚，部位不明) | 硬化性血管腫 |
| | D239(皮膚のその他の良性新生物，皮膚，部位不明) | 軟骨母斑 |
| | D239(皮膚のその他の良性新生物，皮膚，部位不明) | 平滑筋母斑 |
| D31(眼及び付属器の良性新生物) | D310(眼及び付属器の良性新生物，結膜) | 結膜母斑 |
| | D313(眼及び付属器の良性新生物，脈絡膜) | 脈絡膜母斑 |
| | D314(眼及び付属器の良性新生物，毛様体) | 強膜母斑 |
| D48(その他及び部位不明の性状不詳又は不明の新生物 | D485(その他及び部位不明の性状不詳又は不明の新生物，皮膚 | 巨大母斑細胞母斑 |
| | D485(その他及び部位不明の性状不詳又は不明の新生物，皮膚 | 獣皮様母斑 |
| | D485(その他及び部位不明の性状不詳又は不明の新生物，皮膚 | 表在性皮膚脂肪腫性母斑 |
| | D485(その他及び部位不明の性状不詳又は不明の新生物，皮膚 | 分離母斑 |
| H35(その他の網膜障害) | H353(黄斑及び後極の変性) | 網膜血管腫状増殖 |
| I60(くも膜下出血) | I608(その他のくも膜下出血) | 脳動静脈奇形破裂 |
| | I608(その他のくも膜下出血) | 脳動静脈奇形破裂によるくも膜下出血 |
| I61(脳内出血) | I619(脳内出血，詳細不明) | 脳動静脈奇形破裂による脳出血 |
| I78(毛細血管の疾患) | I781(母斑，非新生物性) | くも状血管腫 |
| | I781(母斑，非新生物性) | 体幹老人性血管腫 |
| | I781(母斑，非新生物性) | 老人性血管腫 |

## 別表３　「除外」：集計対象から除外する標準病名（消化管以外の内臓病変、中枢神経病変は除外する）(4/4)

| ICD10小分類 | ICD10細分類 | 標準病名 |
|---|---|---|
| K76(その他の肝疾患) | K764(肝臓紫斑病) | 多発性肝血管腫 |
| O02(受胎のその他の異常生成物) | O028(受胎のその他の明示された異常生成物) | 絨毛血管腫 |
| O99(他に分類されるが妊娠，分娩及び産じょく＜褥＞に合併するその他の母体疾患) | O998(妊娠，分娩及び産じょく＜褥＞に合併するその他の明示された疾患及び病態) | 脳海綿状血管腫合併妊娠 |
| Q24(心臓のその他の先天奇形) | Q249(心臓の先天奇形，詳細不明) | 心臓血管奇形 |
| Q26(大型静脈の先天奇形) | Q268(大型静脈のその他の先天奇形) | ガレン静脈奇形 |
| Q27(末梢血管系のその他の先天奇形) | Q273(末梢性動静脈奇形) | 脊髄髄内動静脈奇形 |
| | Q273(末梢性動静脈奇形) | 脊髄動静脈奇形 |
| | Q273(末梢性動静脈奇形) | 腸動静脈奇形 |
| Q28(循環器系のその他の先天奇形) | Q281(脳実質外血管のその他の奇形) | 海綿静脈洞部海綿状血管腫 |
| | Q281(脳実質外血管のその他の奇形) | 脊髄海綿状血管腫 |
| | Q282(脳血管の動静脈奇形) | 硬膜脳動静脈奇形 |
| | Q282(脳血管の動静脈奇形) | 脳動静脈奇形 |
| | Q283(脳血管のその他の奇形) | 基底核部海綿状血管腫 |
| | Q283(脳血管のその他の奇形) | 基底核部静脈性血管腫 |
| | Q283(脳血管のその他の奇形) | 後頭葉海綿状血管腫 |
| | Q283(脳血管のその他の奇形) | 後頭葉血管腫 |
| | Q283(脳血管のその他の奇形) | 後頭葉静脈性血管腫 |
| | Q283(脳血管のその他の奇形) | 小脳海綿状血管腫 |
| | Q283(脳血管のその他の奇形) | 小脳橋角部海綿状血管腫 |
| | Q283(脳血管のその他の奇形) | 小脳血管腫 |
| | Q283(脳血管のその他の奇形) | 小脳静脈性血管腫 |
| | Q283(脳血管のその他の奇形) | 前頭葉海綿状血管腫 |
| | Q283(脳血管のその他の奇形) | 前頭葉血管腫 |
| | Q283(脳血管のその他の奇形) | 前頭葉静脈性血管腫 |
| | Q283(脳血管のその他の奇形) | 側頭葉海綿状血管腫 |
| | Q283(脳血管のその他の奇形) | 側頭葉血管腫 |
| | Q283(脳血管のその他の奇形) | 側頭葉静脈性血管腫 |
| | Q283(脳血管のその他の奇形) | 側脳室海綿状血管腫 |
| | Q283(脳血管のその他の奇形) | 第三脳室壁海綿状血管腫 |
| | Q283(脳血管のその他の奇形) | 頭頂葉海綿状血管腫 |
| | Q283(脳血管のその他の奇形) | 頭頂葉血管腫 |
| | Q283(脳血管のその他の奇形) | 頭頂葉静脈性血管腫 |
| | Q283(脳血管のその他の奇形) | 脳幹部海綿状血管腫 |
| | Q283(脳血管のその他の奇形) | 脳幹部血管腫 |
| | Q283(脳血管のその他の奇形) | 脳静脈奇形 |
| Q82(皮膚のその他の先天奇形) | Q825(先天性非腫瘍<非新生物>性母斑) | 顔面表皮母斑 |
| | Q825(先天性非腫瘍<非新生物>性母斑) | 結合組織母斑 |
| | Q825(先天性非腫瘍＜非新生物＞性母斑) | 体幹表皮母斑 |
| | Q825(先天性非腫瘍＜非新生物＞性母斑) | 軟性母斑 |
| | Q825(先天性非腫瘍<非新生物>性母斑) | 表皮母斑 |
| Q85(母斑症，他に分類されないもの) | Q858(その他の母斑症，他に分類されないもの) | 頚部表皮母斑 |
| | Q858(その他の母斑症，他に分類されないもの) | 神経母斑症 |
| | Q858(その他の母斑症，他に分類されないもの) | 貧血母斑 |
| | Q859(母斑症，詳細不明) | 基底細胞母斑症候群 |
| | Q859(母斑症，詳細不明) | 脱色素性母斑 |
| | Q859(母斑症，詳細不明) | 母斑症 |
| | Q859(母斑症，詳細不明) | 列序性母斑 |

厚生労働科学研究費補助金（難治性疾患等政策研究事業(難治性疾患政策研究事業)）

分担研究報告書

難治性血管腫・血管奇形・リンパ管腫・リンパ管腫症および関連疾患についての調査研究

# 分担課題

# Lymphatic malformations の診断基準作成、および 希少難治性脈管異常（脈管系腫瘍・脈管奇形）疾患レジストリに関する研究

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研究要旨

脈管異常の国際分類である International Society for the Study of Vascular Anomalies(ISSVA)分類において、いわゆるリンパ管腫（リンパ管奇形)、リンパ管腫症、ゴーハム病、リンパ管拡張症は Lymphatic malformations（LMs）に分類されているが、これらの臨床症状はオーバーラップしており、鑑別が困難な場合が多い。これらの疾患を理解し、正確に鑑別することは的確な治療方針の決定に結び付く。我々はこれらの疾患の特徴をまとめ、診断基準および重症度分類を作成することが目的である。また研究班で取り扱う「希少難治性脈管異常（脈管系腫瘍・脈管奇形）疾患」について、難病プラットフォーム事業の元で、疾患レジストリを作成し、2019 年度に開始する。

LM の鑑別診断法については、これまでの全国調査の症例より各疾患を様々な検査法で鑑別し、来年度に診断基準案を作成するため、その特徴を抽出した。また疾患レジストリについては、本研究班が取り扱う疾患は、未だ疾患の疫学等が不明であるものも多いため、永続的なデータベースとして重要だと考え、難病プラットフォーム事業の中で作成することとする。

Generalized lymphatic anomaly、Kaposiform lymphangiomatosis の違いについて、調査症例をまとめた。またバイオマーカーについても解析し、その病態の違いとの関連性について、国際学会、および国際誌に報告した。これらの結果は診断基準作成の際に、重要な参考所見となるだろう。また疾患レジストリについては、脈管異常は多数の疾患が該当するため、ISSVA 分類を参考に登録疾患の分類を行い、対象疾患を決定した。その後、永続的に調査を行い、役立てるために調査項目を検討し、調査項目を作成した。難病プラットフォーム事務局と連携し、EDC を作成、中央倫理委員会の審査申請を進めている。

## A．研究目的

International Society for the Study of Vascular Anomalies(ISSVA)分類において、リンパ管腫症は Lymphatic malformations（LMs）に分類されている。最近、リンパ管腫症と診断されていた症例の中でも、血胸、凝固異常を起こし、組織に紡錘型細胞の集簇を伴う予後不良な疾患群があることが判明し、Kaposiform lymphangiomatosis(KLA)として分類されている。Generalized lymphatic anomaly（GLA）との鑑別が問題となり、この点について注目した。症例の画像検査、病理学的特徴を参考に、各疾患群に分類した後に、バイオマーカーについても検討する。こうして、疾患の特徴と病態を理解し、正確に鑑別することは的確な治療に結び付けることが出来る。我々はこれらの疾患の特徴をまとめ、診断基準作成することが目的である。

さらに本研究班で取り扱う「希少難治性脈管異常（脈管系腫瘍・脈管奇形）疾患」については、患者数などの疫学情報や臨床的特徴、予後など長期的な疾患登録システムが無いのが現状である。我々は、こうした疾患の対し、永続的なデータベースが今後必要であると考え、「難病プラットフォーム」事業の中で、新たな疾患レジストリを作成することとした。

## B．研究方法

1．LMs の調査研究

（a）全国調査の解析

平成 24、25 年度に行った全国調査以後に情報収集したものの中で、特に鑑別が困難である GLA、KLA について、以下の情報を解析する。

1）基礎情報：生年月、性別、発症時年齢、既往歴、家族歴、2）発症時の症状：骨、胸部（肺、縦隔)、腹部（肝臓、脾臓など)、皮膚、神経、血液、その他、3）経過中に出現した症状、4）診断に使用した画像検査、病理検査、5）予後についてピックアップして解析する。

（b）各疾患の鑑別点の検討

GLA、KLA の臨床症状や特徴的所見を比

較し、どの疾患により頻度が高いかを Fisher's exact test を用いて解析する。また骨病変の数などは the unpaired t test で解析する。

（c）バイオマーカー検索

各疾患の治療前の血漿を凍結保存する。血管新生、リンパ管新生に関わるサイトカイン(ANG1, ANG2, Granulocyte-colony stimulating factor, HB-EGF, HGF, Interleukin-8, Leptin, VEGFA, VEGFC, VEGFD, Angiostatin, sAXL, sc-KIT/sSCFR, eE-Selectin, sHER2, sHER3, sHGFR/sc-MET, Tenascin C, Thrombospondin-2, sTIE2, sVEGFR1, sVEGFR2, sVEGFR3, Platelet-derived growth factor-AB/BB, mTOR)を網羅的に測定し、正常コントロール群、GLA 群、KLA の群での違いを Wilcoxon's rank sum test を用いて解析した。またバイオマーカー候補となったサイトカインの Receiver operating characteristic (ROC)、area under the curve (AUC)を用いて高い感度、特異度となるカットオフ値を算出した。

2.「希少難治性脈管異常（脈管系腫瘍・脈管奇形）疾患」レジストリ作成

本研究班が取り扱っている、希少難治性脈管異常（脈管系腫瘍・脈管奇形）疾患について、前向き、永続的なレジストリシステムを構築する。ISSVA 分類のうち、対象疾患となるものを選定した。また難病プラットフォームに必要な標準項目以外に、臨床像などを調査する項目を検討した。

（倫理面への配慮）

全国調査は複数の医療機関に依頼し、診療情報を調査・集計し、解析して患者数、実際の治療、予後、社会生活レベル等を明らかにし、現在の考え得る最善の治療指針を作成し、また医療全体における当疾患の位置づけを行うことを目的としており、厚生労働省の「疫学研究における倫理指針」の適応範囲に合致する。集計されるデータは、「連結可能匿名化された情報」「観察研究である」「被験者の心理的苦痛を伴わない」ものであると考えられる。人権擁護については厚生労働省の「疫学研究における倫理指針」に準拠しており、プライバシーの保護、不利益・危険性の排除については特に厳守した研究計画を作成する。現計画では倫理問題に抵触する研究は含まれないと考えられるが、研究計画は研究に協力する各施設における倫理審査委員会へ必ず提出し、厳正な審理の後に承認を受けた上で実行に移す。また施行後も岐阜大学倫理審査委員会により、定期的な監査・モニタリングがおこなわれる。

本疫学研究は岐阜大学大学院医学系研究科医学研究等倫理審査委員会にて「難治性血管・リンパ管疾患患者のレジストリシステム構築に関する研究」、「難治性血管・リンパ管疾患患者の臨床学的特徴に関する後方視的研究」として承認済みである。バイオマーカー研究については、「難治性血管・リンパ管疾患患者の疾患特異的マーカー検索およびシロリムス薬理作用に関する研究」として承認済みである。

## C．研究結果

1．LMs の調査研究

（a）GLA、KLA の臨床像の解析

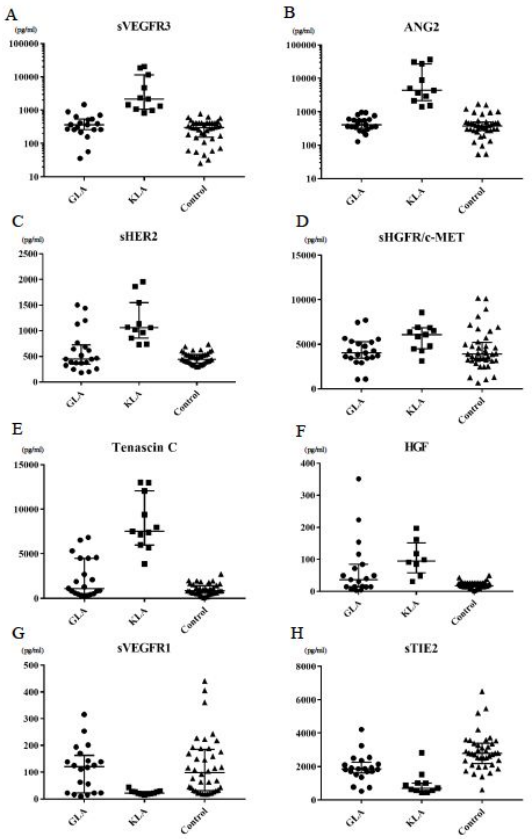
GLA42 例、KLA12 例に対して基礎情報、臨床症状、予後を解析し、統計学的に両者に違いがあるかどうか検証した。GLA は男 13 例、女 29 例に対し、KLA は男 9 例、女 3 例と有意に男性が多かった(p=0.0089)。その他、発症時年齢（GLA の平均は 11.6 歳、KLA6.2 歳）、1 歳未満の症例の割合（GLA34.3%、KLA22.2%）、発症から診断までの期間（GLA 9.7±23.4 か月、0.4±1.0 か月）と有意差はなかった。また家族歴、既往歴は特記すべきことは無かった。

骨病変は GLA の 40.5%、KLA の 50%に認めたが、その特徴に差はなく、骨髄にびまん性に多発する骨溶解病変を認め、骨折は稀であった（GLA 2.4%、KLA 0 %）。胸部（肺、縦隔）病変については、GLA の 85.7%、KLA の 100%に認めた。KLA は縦郭病変が GLA よりも有意に多かった(GLA 28.6%、KLA 75%、p=0.0063)。さらに血性の心嚢水、胸水は KLA に有意に多かった(GLA 14.3%、KLA 66.7%、p＜0.001）腹部（肝臓、脾臓など）については、GLA の 76.2%、KLA の 50%に認めた。多くは脾臓病変であったが、KLA で腹水を認めた症例は無かった。

臨床検査については、特に凝固異常を認めることや多かったが、KLA は 100%に認めたのに対して、GLA は 59.5%と有意に KLA に多かった(p=0.004)。FDP、D-dimer の上昇以外に、重篤な血小板減少（5 万/ul 以下）の症例は KLA に有意に多かった(GLA 11.9%、KLA 66.7%、p＜0.001）。予後は KLA が有意に悪かった(p=0.0268)。

(b)バイオマーカー検索

GLA21 例、KLA の 11 例　の治療前の血漿中サイトカインを測定したところ、KLA の VEGFR3、ANG2、HGF、soluble HER2, tenascin C、soluble HGFR が GLA により有意に高かった。VEGFR3、ANG2 は特に 10 倍以上の差を認めた。反対に、soluble VEGFR1 と soluble TIE2 は KLA が有意に低かった。（図 1）それぞれのバイオマーカーについて、カットオフ値を算出した。




**2.「希少難治性脈管異常（脈管系腫瘍・脈管奇形）疾患」レジストリ作成**

**本研究班で取り扱っている、多数の脈管異常疾患の中で、調査を行う対象疾患をISSVA 分類から選定した。また永続的に基礎情報、臨床症状など調査する項目を作成した。**

**対象疾患は、以下の通りである。**

**脈管系腫瘍**（Vascular tumor）

**・良性脈管性腫瘍**（Benign vascular tumor）

**乳児血管腫**（Infantile hemangioma: IH）PHACE association/syndrome 、LUMBAR (SACRAL, PELVIS) association / syndrome、**先天性血管腫**（Congenital hemangioma）Rapidly involuting congenital hemangioma (RICH) 、 Non-involuting congenital hemangioma (NICH) Partially involuting congenital hemangioma (PICH)、**房状血管腫**（Tufted angioma: TA ） with Kasabach-Merritt phenomenon (TA with KMP) without Kasabach-Merritt phenomenon (TA without KMP)

**・局所侵襲性・境界型脈管性腫瘍**（Locally aggressive or borderline vascular tumors）、**カポジ型血管内皮細胞腫**（Kaposiform hemangioendothelioma: KHE）with Kasabach-Merritt phenomenon (KHE with KMP) without Kasabach-Merritt phenomenon (KHE without KMP)、**網状血管内皮細胞腫** (Retiform hemangioendothelioma) 、Papillary intralymphatic angioendothelioma (PILA) 、Pseudomyogenic hemangioendothelioma

**・肝血管腫**

**乳児血管腫**（Infantile hemangioma）

**先天性血管腫**（Congenital hemangioma）

**脈管奇形**(Vascular malformation)

1) **毛細血管奇形**（Capillary malformations (CM)） **スタージ・ウェバー症候群**（CM with CNS and/or ocular anomalies , Sturge-Weber syndrome）
Diffuse CM with overgrowth (DCMO)
CM of MIC-CAP (microcephaly-capillary malformation) 、 CM of MCAP (megalencephaly-capillary malformation-polymicrogyria)、CM of CM-AVM、**先天性血管拡張性大理石様皮斑**（Cutis marmorata telangiectatica congenita）(CMTC)、**CMのみ**

2) **リンパ管奇形**（Lymphatic malformations (LM))、**難治性嚢胞性リンパ管奇形、リンパ管腫症**、Generalized lymphatic anomaly (GLA)、Kaposiform lymphangiomatosis (KLA)、**ゴーハム病** (Gorham-Stout disease: GSD)、**リンパ管拡張症**（Channel type LM、Central conducting lymphatic anomaly)、**腸管リンパ管拡張症**（Primary intestinal lymphangiectasia: PIL)、**肺リンパ管拡張症**（Pulmonary lymphangiectasia)、"Acquired" progressive lymphatic anomaly (so called acquired progressive "lymphangioma")、**原発性リンパ浮腫**（Primary lymphedema）

3) **静脈奇形**（Venous malformations (VM)）
**難治性静脈奇形**（Venous malformations (VM))、Familial VM cutaneo-mucosal (VMCM)、**青色ゴムまり様母斑症候群**（Blue rubber bleb nevus (Bean) syndrome VM)、Familial intraosseous vascular malformation (VMOS)

4) **難治性動静脈奇形** Arteriovenous malformations (AVM)

5) **難治性混合型脈管奇形**（Combined vascular malformations）

6) **その他**
**他の異常に伴う脈管奇形**（Vascular malformations associated with other anomalies）
**クリッペル・トレノネー・ウェバー症**

候群、Klippel-Trenaunay syndrome、Parkes Weber syndrome 、Servelle-Martorell syndrome、Limb CM + congenital non-progressive limb overgrowth、マフッチ症候群（Maffucci syndrome）、Macrocephaly -CM (M-CM / MCAP) 、 Microcephaly -CM (MICCAP)、クロブス症候群（CLOVES syndrome）、プロテウス症候群（Proteus syndrome ） 、Bannayan-Riley-Ruvalcaba syndrome、CLAPO syndrome、分類不能型脈管異常（Provisionally unclassified vascular anomalies ）、筋肉内血管腫（Intramuscular hemangioma ）、Multifocal lymphangioendotheliomatosis with thrombocytopenia / cutaneovisceral angiomatosis with thrombocytopenia (MLT/CAT)、PTEN (type) hamartoma of soft tissue / "angiomatosis" of soft tissue (PHOST) 、Fibro adipose vascular anomaly (FAVA)

EDC については、EP テクノ株式会社に依頼し作成中である。2019 年 6 月には完成予定である。また内容については中央倫理審査委員会に申請の予定である。

## D．考察

KLA は予後不良であることがわかっており、早期に診断し、適切な治療を行う必要がある。しかし、GLA との区別が困難なことが多い。我々は臨床的特徴以外に、バイオマーカーを調べることによって両者の違いをより明確にする研究を行った。また今後はさらに症例数を増やして検証したい。

また本研究班として、新たな疾患レジストリを作成することとなった。これは未来永劫使用される予定であるが、疾患については ISSVA の中で分類や疾患概念が日々変わっているため、こうした動向にも対応できるような形を目指している。

## E．結論

本研究によって、GLA と KLA の臨床学的差異、およびバイオマーカーが判明した。今後、診断基準作成に活かせるだろう。また新たなレジストリシステムの構築によって、来年度以降にさらに情報収集することが出来るため、より質の高いエビデンスを得られることが予想される。これらは今後の一般診療に還元できるものと思われる。

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**Ｇ．知的所有権の出願・取得状況（予定を含む**

1 **特許取得**

**なし**

2　**実用新案登録**
**なし**

3　**その他**

労働科学研究費補助金（難治性疾患等政策研究事業）
（分担）研究報告書

# 難治性血管腫・血管奇形・リンパ管腫・リンパ管腫症および関連疾患についての調査研究

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研究要旨：研究班の分担研究者として班会議に出席し、班全体の研究活動に関して審議を行った。乳児血管腫の乳児血管腫に対するプロプラノロール療法においては、離乳が完了した児での早朝の低血糖の副作用に特に注意が必要である。

## A．研究目的

長期にわたり患者のQOLを深刻に損なう難治性の病態が含まれる、血管腫・血管奇形・リンパ管腫・リンパ管腫症およびその関連疾患を対象とし、関連各学会、患者団体の意見を統合して提言し、広く医学会・社会の認知を得ることを目的とする。その中で特に、乳児血管腫の治療法について、および、小児から成人への移行期医療について検討する。

## B．研究方法

研究班の分担研究者として班会議に出席し、班全体の研究活動に関して審議を行った。乳児血管腫に対するプロプラノロール療法の副作用について検討した。

（倫理面への配慮）

集計されたデータは、「連結可能匿名化された情報」「人体から採取された試料等を用いない」「観察研究である」「被験者の心理的苦痛を伴わない」ものであった。人権擁護については厚生労働省の「疫学研究における倫理指針」「臨床研究に関する倫理指針」に準拠しており、「人を対象とする医学系研究に関する倫理指針」を遵守した。

## C．研究結果

乳児血管腫に対するプロプラノロール療法における低血糖の発現頻度は0.5%と報告されているが、日本でプロプラノロール製剤が保険承認を得られた後、けいれんをきたすような重篤な低血糖が同程度の頻度で発生していると推定された。

## D．考察

乳児血管腫に対するプロプラノロール療法は、有効性は高いが、まれに心血管系、呼吸器系、および代謝系に重篤な副作用が生じる。その中で、低血糖は最も注意が必要である。特に、1歳を過ぎて離乳が完了し、夜間に哺乳しなくなった児においては、早朝に予期せず重篤な低血糖を生じることがある。空腹時の内服や過量内服を避けるのはもちろんのこと、少しでも体調不良があるときは内服させないこと、離乳食が進んでいる児においては、夕食を早めに摂って薬を内服させ、朝までにもう一度補食するなどの対策をとるように、注意喚起することが必要である。

## E．結論

乳児血管腫に対するプロプラノロール療法においては、低血糖の副作用に特に注意が必要である。

## F．健康危険情報

乳児血管腫に対するプロプラノロール療法において従来の報告と同程度の頻度でけいれんをきたすような重篤な低血糖が発生していると推定された。

## G．研究発表

1．　論文発表

該当なし

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3．　その他

該当なし

## H．知的財産権の出願・登録状況

該当なし

平成 30 年度厚生労働科学研究費補助金　難治性疾患等政策研究事業
難治性血管腫・血管奇形・リンパ管腫・リンパ管腫症および関連疾患についての調査研究（H29-難治等（難）-一般-０１４）

研究分担：普及・啓発、患者療養生活環境整備
平成 30 年度分担研究報告書

分担者　康勝好　埼玉県立小児医療センター血液腫瘍科　科長兼部長
平成 31（2019）年　5 月

**研究要旨：難治性血管腫・血管奇形・リンパ管腫・リンパ管腫症および関連疾患について、療養環境の整備を図るべく小児慢性特定疾病事業において、昨年度新たに脈管系疾患という疾患群を創設することができた。今年度は疾患概念に加えて小児慢性特定疾病の対象疾患となったことについて普及・啓発を行った。主に小児科学会や小児血液・がん学会において、積極的にこれらの疾患について発言、発表を行い、小児科医の啓発に努めた。また乳児血管腫に対するプロプラノロール内服療法についても普及・啓発活動を行った。**

A. 研究目的

疾患概念の形成と啓発、普及、患者に貢献することを目的とする。
特に平成 30 年度は特に昨年度小児慢性疾病に新たに加わった 5 疾患について普及・啓蒙に努める。

B. 研究方法

・小児慢性特定疾病ならびに小児期発症の指定難病との選定、疾病妥当性整理、小児期・成人期移行医療の充実化方策検討を引き続きおこなう。
さらにガイドラインや特定疾病制度について小児科学会や小児血液がん学会において積極的に発表・発言し、普及・啓発に努める。

（倫理面への配慮）

研究はすべてヘルシンキ宣言に則って行われる。患者の個人情報は一切、病院外に漏れることはない。

C. 研究結果

小児慢性特定疾病事業において、昨年度新たに脈管系疾患という疾患群を創設することができた。具体的には、1. 青色ゴムまり様母斑症候群、2. 巨大静脈奇形、3. 巨大動静脈奇形、4. クリッペル・トレノネー・ウェーバー（Klippel-Trenanay-Weber）症候群、5. 原発性リンパ浮腫の 5 疾病である。今年度はこれらの疾病について小児科学会」緒に血液がん学会を中心に普及啓発活動を行った

またこれらの学会に加えて日本レーザー医学会においては、特に乳児血管腫を中心に疾患概念や新たな治療法について普及・啓発することができた。

D. 考察

脈管系疾患については、患者、一般国民のみならず医療者もその疾患概念や自然歴。治療について十分難知識を有していない。このような状況下では小児慢性特定疾病などの制度の拡充を図るとともに、医療者、特に小児科医への啓発・普及が重要である。今年度はこれらの目的において大きな一歩を踏み出すことができた。

E. 結論

今年度の班研究によって、小児慢性特定疾病における脈管系疾患の創設や疾患概念等を小児科医を中心に啓発することができ、大きな成果が得られた、

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**G.知的財産権の出願・登録状況（予定を含む）**

**1. 特許出願**
**なし**
**2. 実用新案登録**
**なし**

**3．その他なし**

厚生労働科学研究費補助金
難治性疾患等政策研究事業（難治性疾患克服研究事業）
分担研究報告書

# 難治性血管腫・血管奇形・リンパ管腫・リンパ管腫症および関連疾患についての調査研究

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【研究要旨】
本研究は血管腫・血管奇形・リンパ管腫・リンパ管腫症およびその関連疾患を対象とする。分担研究者として本研究班の活動を通してリンパ管疾患を中心にガイドラインの普及、英文化、レジストリーシステムの構築、医療関係者や市民への啓発活動を様々な形で行った。

## A．研究目的

本研究は血管腫・血管奇形・リンパ管腫・リンパ管腫症およびその関連疾患を対象とする。これらは長期にわたり患者の QOL を損なう多くの難治性の病態が含まれる。これまでに平成 23 年度難治性血管腫・血管奇形研究班（佐々木班）、平成 24-25 年度同研究班（三村班）、平成 21-23 年リンパ管腫研究班（藤野班）、平成 24-25 年度リンパ管腫症研究班（小関班）、平成 24-25 年度小児期からの消化器系希少難治性疾患研究班の分担研究である腹部リンパ管腫研究、肝血管腫・血管奇形研究を発展させ、相互に協力して疾患概念の形成と啓発、普及、患者に貢献することを目的とする。

## B．研究方法

本研究班の前身である三村班においてリンパ管奇形を加えた形で改訂ガイドラインが 2017 年に完成した。これらを国際的に発信していくために、各領域に分かれて英文論文化し、投稿を行う方針とした。本班研究で扱う疾患群に関してはこれまでレジストリーシステムがなかったために疫学的な実情を把握することが困難であった。この度 AMED 研究のレジストリ構築運営支援として立ち上がった難病プラットフォーム事業に参画することにより、本疾患群のレジストリーシステムを構築する。さらに関係医療者、市民への啓発を進めるために学会におけるシンポジウムや市民公開講座の定期的開催を遂行する。

## C．研究結果

1.ガイドラインの英文化
2017 年に改訂に公開された各領域に分かれて英文論文化し、投稿を行う方針とした。英訳の作業が終了し、投稿前の最終段階となっている。
2.レジストリーシステムの構築
難病プラットフォームと連携したレジストリーシステムの構築をめざし、登録内容の基本骨格の検討を行った。
3.啓発活動
医療関係者や市民への啓発活動として、2018 年 7 月 20 日には日本血管腫・血管奇形学会にて「患者救済の道のり　難病政策と合意形成」というタイトルで患者会の代表の方を交えたシンポジウムを開催した。弾性ストッキングの問題など臨床現場の声が直接届けられる機会を持つことができた。また 2018 年 9 月 29 日には松本市において本班研究の報告会として市民公開講座を行った。さらに関連研究班（藤野班）の活動として 2018 年 9 月 23 日に第 3 回小児リンパ管シンポジウムを行い、研究班を構成する専門家による講演が行われ、市民との交流も行った。

## D．考察

ガイドラインの英文化を具現化できることは本邦から国際的に難病の診療指針について発信できるという意味において大変意義深い。また政策研究班として、疫学的事項の実情が正確につかめていない難病の一群としてレジストリシステムが具体化する方向へ進んでいる状況は他の疾患も含めて本邦難病医療の目指すべき方向性である。市民公開講座は松本市という地方都市で行ったが、予想以上に多くの参加者があり、市民の情報ニーズが感じられた。

## E．結論

二年目の年度においては、政策研究班としての活動がほぼ順調に行えたと考える。今後、時期ガイドラインの改訂、準備中のレジストリーシステムの確立、市民公開講座など患者との接点を意識した班研究活動をさらに促進することを次年度以降の目標とする。

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G．知的財産権の出願・登録状況

該当事項なし

厚生労働科学研究費補助金（難治性疾患等政策研究事業(難治性疾患政策研究事業)）

分担研究報告書

# 難治性血管腫・血管奇形・リンパ管腫・リンパ管腫症および関連疾患についての調査研究

## 診療ガイドラインの改定

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**研究要旨**
2013 年に作成した血管腫･血管奇形診療ガイドラインの改訂のため、H26 年度より clinical question (CQ)を設定し、最新のエビデンスのシステマティックレビューをもとに各 CQ の推奨文や解説の作成を行った。H30 年度は改訂版ガイドラインの英訳を行なった。

### A．研究目的

血管腫・血管奇形・リンパ管腫・リンパ管腫症および関連疾患は難治性の疾患の一つであるが、近年の治療薬の進歩により、ある程度の有効性を示す治療戦略が確立されてきた。しかし、病状によってはそれらの有効性が低くなるのみならず、副作用のため risk-benefit の面で推奨されない可能性もある。

本研究班では 2013 年 2 月に班研究として「血管腫・血管奇形診療ガイドライン」を作成・公表した。そして、厚生労働省研究班の分担研究者と分担協力者などにより最新の EBM に基づいたガイドラインの改定が計画された。この改定版ガイドラインには、血管腫血管奇形の全体像について解説する総説部分と、主に治療の流れを示す「診療アルゴリズム」、診療上の具体的な問題事項である clinical question (CQ)に対する「推奨文」、「推奨度」さらには「解説」よりなる「診療ガイドライン」が記載されている。

本研究事業において我々はガイドライン改定を通じて標準的治療のさらなる周知に努めたい。本研究分担者は乳児血管腫および毛細血管奇形を担当し、本年度は改訂版ガイドラインの英訳を行なった。。

### B．研究方法

①ガイドライン改定の流れ

最初に、ガイドライン作成チームが治療上問題となりうる事項および治療と密接に関連する事項を質問形式で CQ として列挙したものを草案とした。そのリストを委員全員で検討し取捨選択したあと、それぞれの CQ に解答するため、システマティックレビューチームが国内外の文献や資料を網羅的に収集し、システマティックレビューを行った。

続いて、ガイドライン作成チームが再び本邦における医療状況や人種差も考慮しつつ、CQ に対する推奨文を作成した。さらに、Minds 診療グレードに基づいて各推奨文の推奨度を分類した。推奨文の後には「解説」を付記し、根拠となる文献の要約や解説を記載した。例えば文献的な推奨度と委員会が考える推奨度が異なる場合は、エキスパートオピニオンとして「当ガイドライン作成委員会のコンセンサスのもと推奨度を 2D とした」などといった注釈を付けている。

アルゴリズムには上述の CQ を位置づけて診療の流れをわかりやすく図示した。最終的には外部の専門家 2 名に査読を依頼し、さらにはパブリックコメントを広く募集しガイドラインの完成度をさらに高めるべく努力した。また、英訳においては原文のニュアンスの保全に努めた。

（倫理面への配慮）
企業から奨学寄付金は受けているが、文献の解析や推奨度・推奨文の決定に影響を及ぼしていない。

## C．研究結果

改定版ガイドラインの CQ は以下の通りである。

・動静脈奇形

CQ１．動静脈奇形において治療開始時期の目安は何か？

CQ２．動静脈奇形の切除に際して植皮による創閉鎖は皮弁による再建よりも再発（再増大）が多いか？

CQ３．動静脈奇形の流入血管に対する近位（中枢側）での結紮術・コイル塞栓術は有効か？

CQ４．動静脈奇形に対する切除術前塞栓療法の実施時期として、適当なのはいつか？

CQ５．顎骨の動静脈奇形の適切な治療は何か？

CQ６．手指の動静脈奇形の適切な治療は何か？

CQ７．痛みを訴える静脈奇形にはどのような治療が有効か？

CQ８．静脈奇形に対するレーザー照射療法は有効か？

CQ９．静脈奇形に対する硬化療法は有効か？

CQ１０．静脈奇形による血液凝固異常に対して放射線治療の適応はあるか？

CQ１１．毛細血管奇形に対する色素レーザー照射は部位によって効果に差があるか？

CQ１２．毛細血管奇形に対する色素レーザー照射において再発があるか？

CQ１３．毛細血管奇形に対する色素レーザー照射は治療開始年齢が早いほど有効率が高いか？

CQ１４．乳児血管腫に対してプロプラノロール内服療法は安全で有効か？

CQ１５．乳児血管腫における潰瘍形成に対する有効な治療法は何か？

CQ１６．乳児血管腫に対するステロイドの局所注射は全身投与に比べて有効か？

CQ１７．乳児血管腫に対する薬物外用療法は有効か？

CQ１８．乳児血管腫に対して圧迫療法は有効か？

CQ１９．乳児血管腫の診断に免疫染色は有効であるか？

CQ２０．（新規 CQ）青色ゴムまり様母斑症候群（Blue rubber bleb nevus 症候群）を疑った患児には、どのような消化管検査が有用か？また、いつから検査を開始したらよいのか？

CQ２１．血管奇形や症候群で見られる患肢の過成長に対する対応としてどのようなものがあるか？

CQ２２．軟部・体表リンパ管奇形（リンパ管腫）に対する切除術は有効か？

CQ２３．軟部・体表リンパ管奇形（リンパ管腫）に対する適切な手術時期はいつか？

CQ２４．顔面ミクロシスティックリンパ管奇形（海綿状リンパ管腫）に対する硬化療法は有効か？

CQ２５．腹部リンパ管腫に硬化療法は有用か？

CQ２６．臨床症状の乏しい腹部リンパ管腫は治療すべきか？

CQ２７．難治性乳び腹水に対して有効な治療は何か？

CQ２８．腹部リンパ管腫治療における合併症はどのようなものか？

CQ２９．縦隔内で気道狭窄を生じているリンパ管奇形（リンパ管腫）に対して効果的な治療法は何か？どのような治療を行うか？

CQ３０．頚部の気道周囲に分布するリンパ管奇形(リンパ管腫)に対して、乳児期から硬化療法を行うべきか？

CQ３１．舌のリンパ管奇形(リンパ管腫)に対して外科的切除は有効か？

CQ３２．新生児期の乳び胸水に対して積極的な外科的介入は有効か？

CQ３３．難治性の乳び胸水や心嚢液貯留，呼吸障害を呈するリンパ管腫症やゴーハム病に対して有効な治療法は何か？

## D．考察

本ガイドラインでは、現在の血管腫・血管奇形・リンパ管腫・リンパ管腫症の診療現場の状況を十分に熟知した上で、診療上の疑問点・問題点を取り上げ、それらに対して可能な限り具体的な指針が提示されている。医師は常にエビデンスを背景とした最適な医療である evidence based medicine (EBM)を施す事を要求される。しかし、各医師が日常診療の合間に個人的に EBM の手法で情報を収集し評価することは容易でない。最新の文献や情報に基づいた信頼できるガイドラインの存在は臨床的に極めて価値が高いものと考える。本研究班の班員は、業績の豊富な専門家であり国際的に活躍しているため、血管腫・血管奇形・リンパ管腫・リンパ管腫症診療ガイドラインの改訂とさらなる普及による、標準的治療の国内外へのさらなる周知徹底が期待される。

## E．結論

血管腫・血管奇形・リンパ管腫・リンパ管腫症の新しい文献的なエビデンスに基づき診療ガイドラインを改訂し、標準的治療を周知する本研究は国民の健康を守る観点から非常に重要な事業であり、患者 QOL や予後を改善するとともに、患者の不安を取り除く効果も期待される。

## F．研究発表

１．論文発表

（発表誌名巻号・頁・発行年等も記入）

なし

２．学会発表

なし

## G．知的所有権の出願・取得状況（予定を含む

１．特許取得

なし

２．実用新案登録

なし

３．その他

なし

厚生労働科学研究費補助金　難治性疾患等政策研究事業（難治性疾患政策研究事業）
分担研究報告書

# 難治性血管腫・血管奇形・リンパ管腫・リンパ管腫症および関連疾患についての調査研究
# （肝血管腫）

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**研究要旨：深部臓器血管性病変である肝血管腫はこれまでの先行研究で乳児期早期に致死的な経過を取る症例がある事が明らかにされ、乳幼児巨大肝血管腫は難病指定されている。**
**ただし、臨床像や治療実態については未解明の部分が多く、現在全国調査によるリスク因子の把握から、診断基準や重症度分類が整備されつつある。厚労科研田口班の黒田チーム（乳幼児肝血管腫診療ガイドライン作成）と連携し、このガイドライン策定、必要な調査研究、シンポジウム等を通した情報公開を行っている。**

## A．研究目的

深部臓器血管性病変である肝血管腫はこれまでの先行研究で乳児期早期に致死的な経過を取る症例がある事が明らかにされ、乳幼児巨大肝血管腫は難病指定されている。

ただし､臨床像や治療実態については未解明の部分が多く、現在全国調査によるリスク因子の把握から、診断基準や重症度分類が整備されつつある。

当研究班の前身の三村班（平成 26-28 年度）において、血管腫血管奇形・リンパ管奇形診療ガイドライン 2017 を作成し、黒田らはその中にこれまでの研究のまとめとして乳幼児肝巨大血管腫に関する総説を提示した。

次のステップとして病理学的な疾患背景の解明と、海外でもまだ見ない診療ガイドラインの策定を目指している。昨年度からは厚労科研田口班において黒田らは「乳幼児巨大肝血管腫ガイドライン作成に関する研究」を進めており、秋田班における当分担班では藤野が小児外科学会中心の黒田チームと密接に連携しつつ、成人領域へ調査を拡大し、形成外科、放射線科、小児科、皮膚科等の情報を収集する。また以前におこなわれた症例調査（黒田代表）から 5 年経過しており、複数診療科に対して症例調査を計画する。

また研究結果についてはシンポジウムなどを通じて公開し、情報流布に努める。

## B．研究方法

１，田口班黒田チームにおいてガイドライン策定に向けた文献調査を行っており､そちらに､人的協力､情報交換を行う。

２，症例調査研究を行う（黒田チームと共同）

３，関連シンポジウムにて情報公開を行う。

## C．研究結果

１，ガイドライン策定に向けた文献調査をつづけている。昨年度田口班黒田チームにおいて本年度は7つの CQ の策定がされた。今後の推奨文形成において協力することとなっている。

２，これまでの調査で稀少疾患として十分な統計的検討の結果を用いたエビデンスレベルの高い論文は存在しないことが明らかになっている。そのためガイドライン作成における不明瞭点を中心とした症例調査を行うべく項目を検討しているが確定していない。分担研究者のいる国立成育医療研究センターにおいて症例調査を行っており、来年度の第 55 回日本周産期・新生児医学会学術集会にて報告する予定である。

３，平成 30 年 9 月 23 日に国立成育医療研究センター講堂にて第 3 回小児リンパ管疾患シンポジウムが

開催された。その中で研究分担者の木下が「乳幼児肝血管腫ガイドライン」としてこれまでの研究成果の報告をおこなった。

## D．考察

肝血管腫は診療の中では病理学的診断が困難であり、現時点でも詳細な分類を行うに至っていない。臨床的に致死的な場合と、治療に良好に反応する場合があり、これらを鑑別する方法を確立し、ガイドラインとして提供することが重要である。

当研究班においては黒田チームと綿密に連携し、双方からの情報を統合して研究を進めることが望ましい。シンポジウムでの発表などを含めて、現時点では予定通りに進んでいると考える。

## E．結論

肝血管腫の診療ガイドライン作成に向けて厚労科研の 2 班の分担研究チームで連携して研究を進めている。

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**3.その他**

HP：リンパ管疾患情報ステーション
http://lymphangioma.net

## G. 知的財産の出願・登録状況

なし

厚生労働科学研究費補助金（難治性疾患等政策研究事業）
（分担）研究報告書

# 難治性血管腫・血管奇形・リンパ管腫・リンパ管腫症および関連疾患についての調査研究

研究分担者　杠　俊介　信州大学医学部形成再建外科学教室 教授

研究要旨：研究班の分担研究者として班会議に出席し、班全体の研究活動に関して審議を行った。重症乳児血管腫、リンパ管奇形や毛細血管奇形を伴う混合型血管奇形（クリッペル・トレノネー・ウェーバー症候群など）患者へのオーダーメイド弾性着衣の効果を検証した。手術が必要となる乳児血管腫症例の調査を行った。

## A．研究目的

本研究は血管腫・血管奇形・リンパ管腫・リンパ管腫症およびその関連疾患を対象とする。これらの疾患には長期にわたり患者のQOLを深刻に損なう多くの難治性の病態が含まれる。これらの難治性血管腫・脈管奇形に関して、関連各学会、患者団体の意見を統合して提言し、広く医学会・社会の認知を得ることを目的とする。さらに治療法が確立していない難治な病態を呈している患者たちの生活の質を向上するための症状緩和療法や病状コントロールの手法を開発し、それらを患者たちに経済的地理的不利無く提供できるような制度を模索する

## B．研究方法

研究班の分担研究者として班会議に出席し、班全体の研究活動に関して審議を行った。自身が診療している重症乳児血管腫、リンパ管奇形や毛細血管奇形を伴う混合型血管奇形（クリッペル・トレノネー・ウェーバー症候群など）患者にオーダーメイド弾性着衣着用を中心とした複合治療を四肢脈管奇形14名に行った。

プロプラノロール内服療法が導入される以前に、107名の乳児血管腫退縮後にどれくらいの頻度で外見の問題により手術治療が必要になるのか、またどんな手術治療が必要となるのか検討した。

（倫理面への配慮）

集計されたデータは、「連結可能匿名化された情報」「人体から採取された試料等を用いない」「観察研究である」「被験者の心理的苦痛を伴わない」ものであった。人権擁護については厚生労働省の「疫学研究における倫理指針」「臨床研究に関する倫理指針」に準拠しており、「人を対象とする医学系研究に関する倫理指針」を遵守した。

## C．研究結果

1歳までは弾性包帯を使用し、それ以降オーダーメイド弾性着衣着用と漢方薬複合療法を行った。同治療により肥大・浮腫と炎症が抑制され、疼痛と感染コントロールに有効であった。圧をかける場所、ずれないように、子供が自分で装着できるようになど個々にあわせる工夫を必要とした。

乳児血管腫退縮後に外科的切除を実施したのは24例(22.4%)で実施平均年齢は6.2±1.4歳、切除部位は頭頸部が最も多かった(28.9%)。外科的切除を行った症例の中には、部分切除例も認めたが、縫合線を皺線、エステティックユニット、サブユニットに合わせることで、術後瘢痕は目立たず、良好な結果を得た。

## D．考察

脈管奇形は個々に大きさ、症状、部位が異なり、患者の年齢や体格も様々であるため、本人の希望を聴きながら、治療を選択していく必要がある。その中で四肢の巨大な血管奇形に対して、オーダーメイド弾性着衣は比較的導入しやすく、治療における役割は大きいと考えた。同治療は現時点では健康保険に収載されていないため、福祉や公的扶助などの社会制度を含めた患者の生活を継続的に支える制度の整備が重要である。

乳児血管腫の患者では、必要に応じて増殖期に効果的な治療を行い、さらに退縮期に乳児血管腫を部分的にでも切除することで、その後良好な結果を得ることができる。プロプラノロール内服が保険治療となり、今後に手術対象となる患者の動向がどうなるのか疫学的検討が求められる。

## E．結論

難治で重症な混合型脈管奇形の症状緩和に弾性装具は重要で、それを負担なく患者に届ける制度の整備は急務である。プロプラノロール内服による乳児血管腫患者の予後疫学調査が必要である。

## F．健康危険情報

（総括研究報告書にまとめて記入）

## G．研究発表

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3．その他

## H．知的財産権の出願・登録状況

該当なし。

労働科学研究費補助金（難治性疾患等政策研究事業）
（分担）研究報告書

# 難治性血管腫・血管奇形・リンパ管腫・リンパ管腫症および関連疾患についての調査研究

研究分担者　野村　正　神戸大学医学部附属病院形成外科 特命講師

研究要旨：研究班の分担研究者として班会議に出席し、班全体の研究活動に関して審議を行った。重症乳児血管腫、リンパ管奇形や毛細血管奇形を伴う混合型血管奇形（クリッペル・トレノネー・ウェーバー症候群など）患者への局所治療（手術ならびに硬化療法），物理療法，薬物療法の効果を検証した。

## A．研究目的

本研究は血管腫・血管奇形・リンパ管腫・リンパ管腫症およびその関連疾患を対象とする。これらの疾患には長期にわたり患者のQOLを深刻に損なう多くの難治性の病態が含まれる。これらの難治性血管腫・脈管奇形に関して、関連各学会、患者団体の意見を統合して提言し、広く医学会・社会の認知を得ることを目的とする。さらに治療法が確立していない難治な病態を呈している患者たちの生活の質を向上するための局所療法（手術ならびに硬化療法）や物理療法を代表とする病状コントロールの手法を開発し、それらを患者たちに経済的地理的不利無く提供できるような制度を模索する

## B．研究方法

研究班の分担研究者として班会議に出席し、班全体の研究活動に関して審議を行った。自身が診療している混合型血管奇形（クリッペル・トレノネー・ウェーバー症候群など）について手術療法や硬化療法の効果について検討した．稀少疾患のOvergrowth症候群のうち，CLOVES症候群が疑われた症例について遺伝子検査を行った．種々の硬化剤について治療効果と合併症について検討した．

（倫理面への配慮）

集計されたデータは、「連結可能匿名化された情報」「人体から採取された試料等を用いない」「観察研究である」「被験者の心理的苦痛を伴わない」ものであった。人権擁護については厚生労働省の「疫学研究における倫理指針」「臨床研究に関する倫理指針」に準拠しており、「人を対象とする医学系研究に関する倫理指針」を遵守した。

## C．研究結果

Overgrowth症候群のうち，CLOVES症候群が疑われた症例について遺伝子検査を行い，*PIK3CA*遺伝子変異を同定した．また，重症血液貯留型脈管奇形に対する硬化療法において，バーブ付き縫合糸を用いたcompartmentalization法を付加することでより効果的に治療できることが判明した．硬化剤についてはオレイン酸モノエタノールアミン（EO）と泡状ポリドカノール（FPo）を比較したところ，治療効果はEOとFPoで有意差はないもの，合併症発生頻度がFPoで有意に低下した．

## D．考察

本邦でこれまでに報告のないCLOVES症候群症例を報告した．現時点で根治する手立てのない難治性の脈管奇形に対してバーブ付き縫合糸を用いたcompartmentalization法を付加する方法は有効であった．泡状ポリドカノールによる硬化療法は治療効果や合併症の観点から有効であり，本結果は今後の治療開発に寄与できると考えられた。

## E．結論

難治で重症な混合型脈管奇形に対する硬化療法を含む集学的治療は有効であり，さらなる治療方法の開発が急務である。

## F．健康危険情報

（総括研究報告書にまとめて記入）

## G．研究発表

1．　論文発表

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## H．知的財産権の出願・登録状況

該当なし

労働科学研究費補助金（難治性疾患等政策研究事業）
（分担）研究報告書

# 希少難治性血管奇形の実態調査および調査研究

研究分担者　野崎　太希　聖路加国際病院　放射線科　医幹

研究要旨：(とくに青色ゴムまり母斑症候群を中心に)希少難治性血管奇形の指定難病へ向けての診断基準および重症度分類の作成に向けての調査を行った。また、ガイドラインの英文化発刊に向けて日本小児科学会英文誌編集委員会に参加し、3学会(日本小児科学会・日本皮膚科学会・日本医学放射線学会)での同時出版に向けての調整および情報収集を行った。秋田班全体の研究活動に関して審議を行った。

## A．研究目的

本研究は血管腫・血管奇形・リンパ管腫・リンパ管腫症およびその関連疾患を対象とする。これらの疾患のうち希少難治性血管奇形は混合型を含め、原因のまだ同定されていない症候群としても多数知られている。報告数は少なく、正確な患者数は不明である。これらは長期にわたり患者のQOLを深刻に損なう多くの難治性の病態が含まれる。

昨年、小児慢性特定疾患内にいくつかの当班担当疾患であるいくつかの疾患群が認定された。これらの疾患群は小児期から成人期へ移行していくが、指定難病になっていないものが含まれる。症候群を含むこれらの難治性血管腫・脈管奇形に関してはまだ不明な点が多く、診断基準や重症度についてもさらなる調査が必要である。そこで指定難病申請に向けて、情報を収集し、調査していくことを目的とする。それらを当該患者の方々に経済的にも小児期から成人期まで不利なく提供できるような制度構築を模索する。

## B．研究方法

研究協力者の聖路加国際病院小児科副医長　長谷川大輔医師とともにPubmedや医学中央雑誌等の文献調査や学会発表等での報告を検証し、過去のデータから情報を収集した。

研究班の分担研究者として班会議に出席し、班全体の研究活動に関して審議を行った。また、当該疾患は複数の診療科にまたがるが、認知度が低く確定診断に至っていないものが多々あり、コンサルテーションを受けることが多いが、これらを周知すべく、学会等での講演等を通じて啓蒙を行った。また、診療ガイドラインの英文化により世界へ発信していくことも重要と思われ、日本の関連学会3つの同時英文誌出版に向けて、日本小児科学会英文誌編集委員会に編集委員として参加し、情報収集および提案を行った。

（倫理面への配慮）

集計されたデータは、「連結不可能匿名化された情報」「人体から採取された試料等を用いない」「観察研究である」「被験者の心理的苦痛を伴わない」後方視的研究であった。人権擁護については厚生労働省の「疫学研究における倫理指針」「臨床研究に関する倫理指針」に準拠しており、「人を対象とする医学系研究に関する倫理指針」を遵守した。

## C．研究結果

「青色ゴムまり母斑症候群」を含めこれらの症候群を含む希少難治性血管奇形は、全身の多臓器におよぶものが多く、生涯にわたり出血や消費性凝固障害、疼痛などの原因となり、長期間にわたる診療が必要になることが確認された。「青色ゴムまり母斑症候群」の本邦での患者数は100人未満と過去の報告から推定したが、正確な実数はシステムを含め、現時点では限界があり不明であった。

## D．考察

症候群を含む、希少難治性血管奇形の正確な実態調査については文献検索や学会での症例報告では確認できるものの、症例数が少ないため、まとまった原著論文等での報告はほとんどなく、現状のシステムから限界があると考えられる。小児期から成人期へのシームレスな情報提供および経済支援を含めた政策の構築は必要と考えられるが、そのためには今後の難病プラットフォームの疾患レジストリの作成を含め、実態調査が可能となるシステムを構築する必要があると考えられた。

## E．結論

症候群を含む希少難治性血管奇形の患者の正確な実態調査に向けて、難病プラットフォーム、疾患レジストリを構築し、小児期から成人期への移行を含めて、情報提供・経済支援を含めた制度の整備が急務である。

## F．健康危険情報

（総括研究報告書にまとめて記入）

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H．知的財産権の出願・登録状況

該当な

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**資料 1**

# The essence of　Japanese Clinical Practice Guidelines for Vascular Anomalies 2017

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Abstract

The objective was to prepare guidelines to perform the current optimum treatment by organizing effective and efficient treatments of hemangiomas and vascular malformations, verifying the safety, and systematizing treatment, employing the evidence-based medicine (EBM) technique and aimed at improvement of the outcomes. Clinical questions (CQs) were decided based on the following important clinical issues: efficacy of resection, sclerotherapy/embolization, drug therapy, laser therapy, radiotherapy, and other conservative treatment, difference in appropriate treatment due to the location of lesions and among symptoms, appropriate timing of treatment and tests, and

pathological diagnosis deciding the diagnosis. For document retrieval, key words for literature searches were set for each CQ and literatures published from 1980 to the end of September 2014 were searched for in Pubmed, Cochrane Library, and Japana Centra Revuo Medicina (JCRM). The strengths of evidence and recommendations acquired by systematic reviews were determined following the Medical Information Network Distribution System (MINDS) technique and this follows the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines preparation method. Thus, the Japanese Clinical Practice Guidelines for Vascular Anomalies 2017 have been prepared as the evidence-based guidelines for the management of vascular anomalies.

## Introduction

The etiology of vascular anomalies on the body surface and in soft tissue are mostly unclear and no fundamental treatment method has been established. Many patients visit many medical institutions seeking an expert, being a disadvantage in treatment. Hemangiomas and vascular malformations are frequently termed ‘hemangioma’ idiomatically, but these are different diseases in the ISSVA classification proposed by the International Society for Study of Vascular Anomalies (ISSVA),[1, 2] and this classification has been internationally standardized.

‘Clinical practice guidelines for vascular anomalies 2013’ (1st edition)[3] target general practitioners and the general public and were prepared aiming at organizing effective and efficient treatments for hemangiomas/vascular malformations, verifying the safety, and systematizing treatment using the evidence-based medicine (EBM) technique. The organization responsible for preparation was the Health, Labour and Welfare Sciences Research Grants (Research on Measures for Intractable Diseases), Research Committee for ‘Intractable Vascular anomalies’, and the main

committee members were selected from academic societies of plastic surgery and radiology mainly treating hemangiomas and vascular malformations: the Japanese Society of Plastic and Reconstructive Surgery and Japanese Society of Interventional Radiology, and the guidelines were prepared by them.

‘‘Clinical practice guidelines for vascular anomalies 2017’ were prepared as a revised edition of the ‘Clinical practice guidelines for vascular anomalies 2013’. The organization responsible for preparation was the Health, Labour and Welfare Sciences Research Grants (Research on Policy Planning and Evaluation for Rare and Intractable Diseases), Research Committee for Intractable Vascular Anomalies, and the difference from the previous guidelines is setting the objective at summarizing opinions from related academic societies by inviting many committee members from dermatologists, pediatric surgeons, pediatricians, radiologists (diagnostic radiology), and basic researchers including the pathology, molecular-biology, and epidemiology fields, in addition to plastic surgeons and radiologists (interventional radiology). Since the guidelines were prepared following the reformed ‘Minds Handbook for Clinical Practice Guideline Development 2014’[4] and ‘Minds Manual for Clinical Practice Guideline Development Ver.1.0-2.0’,[5, 6] it was fully revised.

The original text of the guidelines (Japanese version) is comprised of Reviews and Clinical Questions (CQs), but only CQs are presented in this report.

**Purpose of the guideline**

The objective was to prepare guidelines to perform the current optimum treatment by organizing effective and efficient treatments of hemangiomas and vascular malformations, verifying the safety, and systematizing treatment, employing the evidence-based medicine (EBM) technique and aimed at improvement of the following outcomes: Pain, swelling, esthetic impairment, and

functional disorder.

**Funders and conflict of interest**

The fund for preparation of the Japanese Clinical Practice Guidelines for Vascular Anomalies 2017 was from 2014-2016 Health, Labour and Welfare Sciences Research Grants (Research on Policy Planning and Evaluation for Rare and Intractable Diseases) provided to ‘Japanese Research Committees for Intractable Vascular Anomalies’ (main funding source), ‘Japanese Study Group for Intractable Diseases of Pediatric Gastrointestinal Tract’, and ‘Japanese Research Committees for Survey and Establishment of Guidelines for Pediatric Respiratory Dysplastic/hypoplastic Disease’. No financial support was received from any other organization or corporation. Conflict of interest of the guideline preparation organization was managed by the Guideline Executive Committee. The following corporations were disclosed by self-declaration of the Guideline Committee members in the 3 year-period before 1 April 2017. Japan Pharmaceuticals and Medical Devices Agency (PMDA), Mitsubishi Foundation, Rohto Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation, and Shionogi & Co., Ltd.

**Materials and Methods**

Organization

For the Guideline Executive Committee members, representatives of the plastic surgery, dermatology, radiology, pediatric surgery, and basic science fields were selected. The guideline preparation group and systematic review team for preparation of CQs and recommendations were comprised of 4 groups: groups in charge of arteriovenous malformation (AVM), venous malformation (VM), combined type, and syndrome, in charge of capillary malformation and infantile hemangioma, in charge of the lymphatic malformation (lymphangioma) (LM), and in

charge of the basic field. To the group in charge of AVM, VM, combined type, and syndrome, plastic surgeons and radiologists were mainly assigned. To the group in charge of capillary malformation and infantile hemangioma, plastic surgeons and dermatologists were mainly assigned. To the group in charge of the lymphatic system, pediatric surgeons, plastic surgeons, and pediatricians were mainly assigned. The Reviews of the guidelines were also prepared by those selected from each group. Pathologists and molecular-biologists were in charge of the Reviews of the basic fields.

Preparation process

The guidelines were revised following the 'Minds Handbook for Clinical Practice Guideline Development 2014' and 'Minds Manual for Clinical Practice Guideline Development Ver.1.0-2.0'

CQs were decided based on the following important clinical issues: 1) Efficacy of resection, 2) efficacy of sclerotherapy/embolization, 3) efficacy of drug therapy, laser therapy, radiotherapy, and other conservative treatment, 4) difference in appropriate treatment due to the location of lesions, 5) difference in appropriate treatment among symptoms, 6) appropriate timing of treatment and tests, 7) pathological diagnosis deciding the diagnosis.

For document retrieval, key words for literature searches were set for each CQ and literatures published from 1980 to the end of September 2014 were searched for in Pubmed, Cochrane Library, and Japana Centra Revuo Medicina (JCRM). Literature search was requested to the Japan Medical Library Association. For decisions on CQs and recommendations lacking evidence or having weak evidence, discussion and agreement in the preparation group were reflected.

The strengths of evidence and recommendations acquired by systematic reviews were determined following the Minds technique as described below and this follows the GRADE guidelines preparation method.[7, 8]

Determination of the Strength of Evidence of the Body of Evidence (Table)

The Strength of Evidence of the Body of Evidence was determined according to ‘Minds Handbook for Clinical Practice Guideline Development 2014’.

In the case of RCTs, the score “A (strong)” is given at the start of evaluation, and the final score might be downgraded to B, C, or D, according to the results of evaluation of five items, including risk of bias, inconsistency in results, indirectness of evidence, data imprecision, and high possibility of publication bias. In the case of observational studies, the score “C (weak)” is given at the start of evaluation, and five items lowering the strength are evaluated similarly as for RCTs. In addition, three items, including large effect with no confounding factors, dose–response gradient, and possible confounding factors, are weaker than actual effects increasing the strength are evaluated as well.

Presentation of the strength of recommendations (Table 1)

The strength of recommendation was also determined according to ‘Minds Handbook for Clinical Practice Guideline Development 2014’.

The strength of recommendations is usually presented in two ways: “1”: strongly recommended, and “2”: weakly recommended (suggested). If the strength of recommendations cannot be determined by any means, it is occasionally presented as “no definite recommendation can be made.” Recommendations will be entered as follows by putting down the strength of evidence (A, B, C, D) with the strength of recommendations “1”: strong or “2”: weak.

Finalization

Preparation of the draft guidelines was completed in December 2016 and review was requested to the Japanese Society of Plastic and Reconstructive Surgery, Japanese Dermatological Association, Japan Radiology Society, Japanese Society of Interventional Radiology, Japanese Society of Pediatric Surgeons, and Japanese Society of Pathology between December 2016 and January 2017, and corrections were made based on the results of the reviews. In addition, from December 2016 to January 2017, the guidelines were disclosed on the home page of the Research Committee for 'Intractable Vascular Anomalies' and public comments were collected. The draft guidelines were presented to 2 related patient organizations, 'the Patients Association of Vascular Anomalies' and 'the Patients Association of Combined vascular malformations' and comments were received. Based on these, the draft guidelines were brushed up and CQs, recommendations, and explanations were completed. It was finalized in March 2017.

## Results

### CQs and recommendations

CQ1: What is the guideline for the time to begin treatment for AVM?

Recommendation:

It is necessary to judge the time to begin endovascular or surgical treatment for AVM individually by evaluating the stage of symptoms and lesion extent and in consideration of the risk of complications.

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| Strength of recommendation | 2 (weak) |
| Evidence | D (very weak) |

Comments

As a result of primary screening, 92, 3, and 27 papers were extracted from PubMed, JCRM, and Cochrane Library, respectively, and, as a result of secondary screening, 37 and 3 papers were extracted from PubMed and JCRM, respectively. However, as all these references were observational or case series studies, the strength of evidence is rated as “D (very weak)”.

There has been no report in which the time to begin treatment for AVM in itself was the endpoint, and only some reports described the view on the time to begin treatment in the discussion. Therefore, as it is difficult to objectively evaluate the validity of the time to begin treatment, we surmised whether or not a guideline can be derived from the patient age, lesion site, symptoms, clinical stage, effectiveness of treatment, frequency of complications in each report.

In the reports on the treatment for AVM, symptomatic AVM is primarily addressed, and treatment can be reserved (follow-up) while the lesion remains asymptomatic. However, as AVM often progresses when left untreated, it is considered important to begin the treatment at an appropriate time depending on the stage of symptoms. In addition, as there is the tendency that the response rate decreases, and the complication rate increases, with progression of symptoms, some reports from particular pediatric institutions where patients are concentrated recommend early therapeutic intervention in relatively “early” or “mild” stages without waiting for progression of the disease.[9, 10]

Localized lesions may be radically treated by early intervention.[11] Among endovascular procedures, the response (cure) rate tends to be high by ethanol embolization, but as the complication rate is also high, benefit and harm are matched.[12, 13] By surgery, localized lesions are unlikely to recur if they are completely resected, although adverse events such as postoperative cicatrization/deformation or functional impairment has been seldom discussed.[10] On the other hand, in diffuse lesions, limitations of effectiveness such as recurrence and persistence and the risk of treatment are higher by both endovascular treatment and surgery, and harms may surpass benefits.[13]

It should also be considered that children, in particular, are not mentally ready to accept such invasive treatments.[14]

As discussed above, it is difficult to give a guideline for the time to begin treatment for AVM at present, and individual judgment is necessary depending on the symptom stage and lesion extent in consideration of the complication risk.

CQ2: Is recurrence (regrowth) after resection of AVM more frequent by wound closure with a skin graft than by reconstruction using a flap?

Recommendation:

Whether or not recurrence (regrowth) is more frequent by wound closure with a skin graft compared with reconstruction using a flap is unclear.

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| Strength of recommendation | 2 (weak) |
| Evidence | D (very weak) |

Comments

The number of references retrieved by searches using keywords was 40 from JCRM, 75 from PubMed, and 0 from Cochrane, and 39 were extracted by secondary screening. For AVM with a certain size, reconstruction is necessary after resection, and wound closure by skin grafting or reconstruction using a flap is selected according to common reconstruction methods for tissue defects. The reports discussing reconstruction after resection of AVM that we could retrieve were all descriptive studies (case reports or case series studies). Therefore, the evidence level of all these references is D (very weak).

The concept of regulating flap,[15, 16] that reconstruction using a free flap controls the

recurrence or regrowth after resection of AVM, has been proposed. However, no report has evaluated whether or not free flaps[16-37] and other flap types[17, 19, 25, 28, 38-49] clearly suppress the recurrence or regrowth compared with skin grafts.[21, 23, 50-52]

According to the present knowledge about the recurrence or regrowth after resection of AVM,[15, 16, 39, 53] whether or not AVM can be completely resected is important, and, concerning cases in which complete resection is difficult, it has been reported that the hemodynamics in the residual lesions contributes to the recurrence and regrowth and that it can be controlled by a flap with rich blood flow.

CQ3: Is proximal ligation/coil embolization of the feeding artery of AVM effective?

Recommendation:

The therapeutic effect of ligation/coil embolization of the feeding artery on the proximal side may be poor, and the possibility of recurrence may be high. In addition, in the event of recurrence, treatment may become difficult due to the development of collateral vessels. Therefore, these procedures are recommended to be avoided, in principle.

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| Strength of recommendation | 2 (weak) |
| Evidence | D (very weak) |

Comments

As a result of secondary screening, 1 and 14 papers were extracted from PubMed and JCRM, respectively, and were reviewed. As a result, all these papers were case reports. In addition, 6 papers retrieved by manual searches were also reviewed, but they were all case series studies at the maximum. Therefore, the strength of evidence as a collection of literature concerning this CQ is D

(very weak).

To summarize the evaluation of this collection of papers, AVM was treated by proximal ligation/coil embolization of the feeding artery, but as there have been reports of recurrence following the development of collateral channels (reports of cases of the occurrence of unfavorable situations), the treatment is recommended to be avoided, but the evidence level of this recommendation is low as mentioned above.

The objective of embolization for AVM is obliteration of the nidus, and embolization at or near the nidus is necessary as much as possible. If ligation/coil embolization of the feeding artery is performed on the proximal/central side, the nidus is not obliterated, and the development of multiple collateral channels is promoted. In many cases, the collateral channels are thin, complicated, and markedly tortuous, and trans-catheter treatment is often difficult.

Wu et al. reported that they performed proximal ligation in 9 of 29 patients treated for AVM of the auricle but that the condition was exacerbated in all patients with 8 requiring auricular resection and 1 requiring additional treatment. They excluded proximal ligation from treatment options for AVM, because it makes subsequent trans-catheter treatments difficult.[14]

Slaba et al. evaluated 25 patients with AVM of the tongue and reported that 3 of the 12 symptomatic patients who underwent ipsilateral external carotid artery ligation at another facility showed marked development of collateral channels.[54]

Other reports include those of a case in which a large number of collateral channels developed as a result of ligation of the feeding artery for AVM of the shoulder with serious complications including high-output heart failure,[55] 3 cases in which proximal ligation/embolization was performed for AVM of the limbs and pelvis, collateral vessels developed, but the condition could be controlled by multidisciplinary treatment consisting of trans-catheter treatment and direct puncture sclerotherapy,[56] and multiple cases in which external carotid artery ligation was performed

for AVM of the head and neck, but the subsequent treatment was difficult.

Suyama et al. reported a case in which AVM of the auricle, treated by proximal embolization using coils and gelatin sponge, recurred and was treated again by ligation at a proximal part of the artery, but the lesion recurred again.[35] Also, Aikawa et al. reported a case of intrapelvic AVM that underwent coil embolization of the left ovarian artery and left internal iliac artery but showed little change in the area of the nidus or the state of arterial or venous dilatation.[57] In addition, Yamamoto et al. reported a case in which TAE was performed for AVM of the mandible via the maxillary artery, facial artery, lingual artery, and ocular artery but was not effective due to the development of collateral channels from the internal carotid artery and vertebral artery.[58]

As observed above, it is recommended not to select proximal/central ligation/coil embolization as a treatment for AVM. However, AV fistulas with direct connection of a large artery and a vessel may be treated by coil embolization if the shunt area is directly accessible with a catheter. Proximal coil embolization may also be accepted as preoperative embolization, but careful evaluation of its indications is necessary, and embolization at a site near the shunt is desirable to leave the room for catheter insertion in the event of future recurrence.

CQ4: What is the appropriate timing for embolization before resection of AVM?

Recommendation:

It is recommended to perform resection within 3 days (72 hours) after embolization. If the interval prolongs, the risk of massive intraoperative hemorrhage may increase due to recanalization of the embolized vessel and development of collateral channels. In addition, surgery has been reported to be made difficult by enlargement of the lesion after embolization.

Strength of recommendation 2 (weak)

Evidence D (very weak)

Comments

While it is difficult to generalize the therapeutic approach as it varies with the affected area and extent of the lesion, there were a few reports that preoperative embolization was useful for the treatment of AVM of the head and neck region.

As a result of secondary screening, 10 and 3 papers from PubMed and JCRM, respectively, were reviewed. All the papers selected by this screening procedure were case reports or case series, and the strength of evidence is “D (very weak)”. Mentions about the timing of preoperative embolization and volume of hemorrhage also varied among the papers. Although it is difficult to draw a conclusion, among the papers that mentioned specific timing of preoperative embolization and volume of hemorrhage, Deng et al. performed embolization within 48-72 hours before surgery in 16 patients with maxillofacial AVM and reported that the volume of hemorrhage was ≤200 mL in all patients and that there were no complications.[59] Erdmann et al. performed embolization within 24 hours before surgery in 4 patients with head and neck AVM, and the lesion could be resected with hemorrhage of ≤100 mL in 3.[60] It is recommended to perform resection within 72 hours to prevent increases in difficulty of resection due to inflammation after embolization.

There have also been reports that embolization was performed intraoperatively or within a few days before surgery, resulting in decreases in the volume of hemorrhage or favorable long-term outcomes. Most papers reported no or only mild complications, but as for relatively severe complications, Goldberg et al. reported temporary visual impairment in 2 of the 3 patients with orbital AVM.[61]

Factors that affect the appropriate timing of preoperative embolization include recanalization of the target vessel, development of collateral channels, and swelling and reactive

changes after embolization, which make surgery difficult. To avoid the effects of these phenomena, many papers supported relatively early resection, i.e., within 72 hours after embolization. Clinically, also, there is no benefit in taking a long interval, and it is considered valid to recommend resection within 72 hours after embolization.

In conclusion, adequate control of hemorrhage may be achieved with fewer complications by performing vascular embolization within a few days before surgery, but no sufficient evidence that support this view has been provided.

CQ5: What are appropriate treatments for the maxillo-mandibular AVM?

Recommendation:

Although surgery alone is not recommended, a combination of surgery with endovascular embolization (including sclerotherapy) can be recommended depending on the case.

Radiotherapy is not recommended.

Endovascular embolization (including sclerotherapy) alone or as a preoperative treatment can be recommended.

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| Strength of recommendation | 2 (weak) |
| Evidence | D (very weak) |

Comments

AVM of the maxilla and mandible is a rare disorder. Most of the literature is reports of a small number of cases except a few case series reported from some special institutions. Only 5 reports of a series of 10 or more cases were retrieved by the search of PubMed.[62-66] Because there is no cohort study or randomized trial comparing various treatments, strong evidence regarding the best

treatment is absent.

Maxillo-mandibular AVM may involve the maxilla, mandible, or both, and it often presents with massive oral hemorrhage around the age of 10 years when milk teeth are lost, but may also be detected due to swelling of the soft tissue, etc.

According to Persky et al., embolization alone resulted in cure in 42%, improvement in 16%, and stabilization of symptoms in 23% of the 26 patients with a maxillo-mandibularAVM.[62] Liu et al. treated 25 patients by transarterial or transvenous embolization alone or in combination with curettage and reported anatomical cure in 14 and clinical cure in 21.[63] Chen et al. treated 15 patients by bone wax packing (BWP) alone in 4, transarterial embolization (TAE) + BWP in 3, TAE + resection in 4, and TAE + radiotherapy + resection in 4 and reported clinical cure in 14.[65]

The following are considered as treatment options for AVM of the maxilla and mandible.

A: Surgical treatment

A-1: Resection and reconstruction

A-2: Curettage

A-3: Bone wax packing

B: Endovascular embolization (including sclerotherapy)

B-1: Transarterial embolization

B-2: Transvenous embolization

B-3: Embolization by direct puncture

C: Combination of A and B

D: Radiotherapy

The literature is mostly about B, i.e., endovascular embolization (including sclerotherapy) alone, or surgical treatment after B. There was no report of case series of surgical treatment alone, but there was only 1 report of case series of surgery + radiotherapy.[65] Surgery alone and radiotherapy

are generally not recommended. Endovascular embolization is performed by various approaches including transarterial and transvenous routes and direct puncture, sometimes, in combination. Concerning embolic agents, PVA and Gelfoam are used for embolization as an adjuvant therapy immediately before surgery as they tend to recanalize after some time. Cyanoacrylate liquid embolic agents are considered effective for embolization performed preoperatively or alone in expectation of a long-term occlusive effect.[64, 67, 68] Coils are often used for transvenous embolization. Recently, there have been reports that favorable outcomes could be obtained by TAE using Onyx, a non-adhesive liquid embolic agent.[69, 70] Concerning sclerotherapy, there is a case series study of ethanol sclerotherapy alone, reporting relatively favorable outcomes.[71] Infection and bone necrosis are frequent complications of embolization, and they tend to occur, when an embolic agent, a foreign body, is injected into lesions that have developed communication with the external environment due to direct puncture or hemorrhage. Surgical treatments as listed above are performed primarily after endovascular embolization. Invasive radical resection and reconstruction should be avoided at least as the initial treatment, because many lesions are nowadays controlled by endovascular embolization alone with the advancement of endovascular technique.

As mentioned above, endovascular embolization is performed using various approaches and embolic agents selected depending on the facility and patient. There are also a wide variety of surgical treatment options. Since the treatment may be performed by combining these options, AVM of the maxilla and mandible should be treated at the institutions where multidisciplinary treatment can be performed by experienced physicians.

CQ6: What are appropriate treatments for AVM of the fingers?

Recommendation:

Although embolization or sclerotherapy is effective as it alleviates symptoms, such as pain,

sufficient evaluation is necessary because of the risk of finger necrosis and nerve damage. In surgical resection, total resection is recommended, because partial resection is likely to permit enlargement of the lesion. Occasionally, the disorder results in finger amputation.

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| Strength of recommendation | 2 (weak) |
| Evidence | D (very weak) |

Comments

As a result of primary screening, 38, 16, and 35 papers were retrieved from PubMed, Cochrane Library, and JCRM, respectively. However, during secondary screening, many reports observed concerned AV shunts in dialysis patients and AVM at sites other than the fingers. Eventually, only 10 papers consisting of 3 case series and 7 case reports remained as references, and the evidence level is extremely low (D: very weak).

AVM of the fingers is often difficult to treat, and treatments are likely to be ineffective, particularly, when the lesion extends from the fingers to the palm. In addition, when AVM is localized in the fingers, complications are likely to occur after treatment.[72] It is recommended to conduct treatment by a team from multiple departments including the plastic surgery, vascular surgery, and radiology departments.[73] 3D-CTA is useful for preoperative examination.[74] Since complete cure is difficult to obtain by embolization therapy, it is recommended to be performed for alleviation of symptoms such as pain only in symptomatic areas.[75] In addition, as there is the possibility of re-enlargement after embolization, it is recommended to periodically follow-up the condition and repeatedly perform embolization each time symptoms appear.[73] Surgical resection is necessary for permanent cure, and total resection is recommended as there is the possibility of re-enlargement after partial resection.[76-78] Reconstruction is occasionally necessary, but treatment

may end in finger amputation. In this event, preoperative embolization or sclerotherapy is effective.[79] The present review has fallen short of clarifying situations in which preoperative embolization is useful in fingers to which a tourniquet can be applied.

CQ7: What treatments are effective for painful VMs?

Recommendation:

Sclerotherapy, surgical resection, etc., as well as conservative treatments, such as compression, oral aspirin, and low-molecular-weight heparin, are reported to be effective depending on the site and size of the lesion and symptoms. Endovascular laser treatment, percutaneous cryotherapy, and photodynamic therapy have also been suggested to be effective.

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| Strength of recommendation | 2 (weak) |
| Evidence | D (very weak) |

Comments

As a result of literature search, 54 reports in English and 4 in Japanese were retrieved by primary screening.

Of these reports, 39 in English and 4 in Japanese were extracted by secondary screening. Many options were enumerated as treatments for pain associated with VMs, but all these documents were case series or case reports without comparison of treatments. Therefore, the evidence level was rated as “very weak”, and the recommendation level as “weak”.

Pain is one of the major symptoms of VMs. It may respond to conservative treatments that are relatively easy to manage such as compression and oral aspirin depending on the site and size of the lesion and symptoms. Particularly, when pain is localized, surgery should also be considered.

Relatively novel treatments, such as endovascular laser therapy, percutaneous cryotherapy, and photodynamic therapy, have been reported to be effective for controlling local VMs, and they have also been reported to be effective for the control of pain. Limb lesions accompanied by localized intravascular coagulopathy (LIC) may be indications for low-molecular-weight heparin. Reports on various treatments are mentioned below.

(1) Compression

Although there has been no report of comparative evaluation, compression is reportedly effective according to reviews by specialized medical facilities.[80-82]

(2) Oral aspirin

The literature is also limited, but the treatment has been mentioned in reviews.[80-82] Nguyen et al. reported that pain was alleviated in 17 (77%) of 22 patients in whom oral aspirin therapy was initiated for pain.[83]

(3) Sclerotherapy

Sclerotherapy has often been performed using ethanol or polidocanol. The literature concerning other sclerosing agents is scarce, and their effectiveness remains largely unclear.

Each sclerosing agent is commented below.

(i) Ethanol

Shireman et al. reported remission in 6 (50%) of 12 patients,[84] and Rimon et al. reported alleviation or remission in 14 patients with painful VMs (including 8 with lower limb lesions) except in 4 with lower limb lesions.[85] Marrocco-Trischitta et al. reported that pain was resolved in both (100%) of 2 women with external genital lesions.[86]

Concerning the use of ethanol, Suh et al. reported alleviation to 50% or less of the pre-treatment state according to a VAS in 12 (71%) of 17 patients who underwent sclerotherapy using its mixture with lipiodol,[87] and Dompmartin et al. reported 37 patients who underwent

sclerotherapy using its mixture with ethylcellulose.[88] According to Schumacher et al., also, 77 patients underwent sclerotherapy using ethylcellulose-ethanol in a multicenter study,[89] and significant improvement compared with the pre-treatment state was observed in all patients.

(ii) Polidocanol (including foam sclerotherapy)

Mimura et al. reported remission in 6, alleviation in 4, and no change in 1 of 11 patients with painful VMs,[90] and remission in 12 (41%), alleviation in 14 (48%), no change in 2 (7%), and exacerbation in 1 (3%) of 29 patients in another study.[91] Cabrera et al. treated 50 patients (including 15 with Klippel-Trenaunay syndrome) using a foamed sclerosing agent and reported remission in 25 (50%) and alleviation in 14 (28%).[92] Marrocco-Trischitta et al. reported resolution of pain in all 3 women (100%) with external genital lesions.[86]

(iii) Ethanolamine oleate

Ozaki et al. reported remission in 2 (20%) and alleviation in 8 (80%) of 10 patients.[93]

(iv) Sodium tetradecyl sulfate

Krokidis et al. reported alleviation of pain in 4 (80%) of 5 women with external genital lesions.[94]

(4) Surgical resection

Enjolras et al. performed surgical resection in 7 of 13 patients with VMs involving a wide area including the knee joint and reported alleviation of pain in 5 (71%).[95] Steiner et al. reported alleviation to 50% or less of the pre-treatment state by a VAS in 24 (89%) of 27 patients with background pain and 12 (92%) of 13 patients with acute episodic pain.[96] In addition, Noel et al. performed surgical resection and compression therapy for VMs of the lower extremities in 20 patients with Klippel-Trenaunay syndrome and reported disappearance of pain in 18 (90%) (mean follow-up period: 63 months).[97]

(5) Endovascular laser therapy

Sidhu et al. and Lu et al. reported alleviation of pain in all 8 and 51 lesions in 6 and 33 patients, respectively.[98, 99] Liu et al. also reported marked responses in 46 (35%), responses in 84 (63%), and no change in 3 (2%) of 133 patients.[100]

(6) Low-molecular-weight heparin

According to Mazoyer et al., only low-molecular-weight heparin was effective when VMs are complicated by localized intravascular coagulation (LIC), resulting in disappearance of pain.[101]

(7) Percutaneous cryotherapy

Cornelis et al. reported remission of pain in a report of 1 case (observation period: 2 months) and a report of 4 cases (observation period: 6 months).[102, 103]

(8) Photodynamic therapy

Betz et al. reported remission in 2 (67%) and alleviation in 1 (33%) of 3 patients.[104]

CQ8: Is laser therapy effective for VMs?

Recommendation:

With appropriate selection of the type of laser according to the site, size, and symptoms of the lesion, laser therapy can be effective for the treatment of VMs. It is recommended to evaluate whether the net benefit by laser therapy matches the cost and resources by comparison with other treatments such as sclerotherapy and surgical resection.

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| Strength of recommendation | 2 (weak) |
| Evidence | C (weak) |

Comments

VM is a lesion that has been called cavernous hemangioma, and it causes pain, functional

impairment, and cosmetic defect depending on the affected site. In addition to conventional resection of the lesion, sclerotherapy has been widely performed in recent years. While reports of laser therapy for VMs have increased, there have not been prospective studies comparing the results of laser therapy with those of surgery or sclerotherapy, among types of laser equipment different in wavelength, or using the same equipment type but changing the irradiation method or parameter setting. We analyzed 134 papers extracted by primary screening and 98 papers extracted by secondary screening. Concerning more than 30 cases the answer to the CQ was based primarily on 7 reports summarizing the methods and sites of treatment and benefits and harms derived from treatment (decrease in size of the lesion, alleviation of symptoms, complications).

In the facial skin, pigmentation and scar formation after irradiation can be serious treatment-related complications compared with unexposed areas. In the airway and digestive tract, the mass effect of the lesion and chronic bleeding from the lesion can be causes of serious symptoms. Thus, as the goal to achieve varies with the anatomical site of the lesion, we reviewed the literature by the anatomical site (the neurosurgery field was excluded). For this reason, we also extracted benefits and harms of treatment from the text of the reports of less than 30 cases. The relevant departments surveyed included ENT, dental and oral surgery, gastrointestinal surgery, ophthalmology, plastic surgery, and dermatology, and secondary screening overviewed laser therapy for VMs and vasodilatory lesions.

When a new laser instrument is developed and put into use, reports of therapeutic results using the equipment are presented. The types of laser used for treatment varied widely. The types of laser that have been reported are summarized chronologically in a graph (Figure 1). While the type of laser with more reports is not necessarily more effective, the graph is considered to reflect tendencies of laser types that are established and gain favorable appraisal or have fallen into disuse.

Since dye laser used for the treatment of port wine stain (wavelength: 595 nm) uses

hemoglobin as the observer/heater, photothermal conversion occurs efficiently in the blood vessel, and the thermal energy reaches endothelial cells.[105] However, its optical penetration depth is shallow, being about 1 mm in both the skin and mucosa.[105] However, in Nd:YAG laser with a longer wavelength (1064 nm), the optical penetration depth is about 3 mm in the skin and about 6 mm in the mucosa.[105] Although Nd:YAG laser is advantageous compared with dye laser for the treatment of deep lesions, heat is generated also in perivascular tissues, because light is converted to heat as it is absorbed by water contained in the skin and mucosa.

The target of laser treatment for VMs is the endothelium of morbidly dilated blood vessels. There is no light that is specifically absorbed by endothelial cells and emits heat. Satisfactory therapeutic results cannot be expected unless treatment is performed by selecting the laser type and modifying the irradiation method based on the understanding of such principles and limitations of phototherapy.

Concerning small VMs of the mucosa, tongue, lips, and glans penis, in which scar formation after treatment poses no serious problem, there are a number of reports that lesions could be resolved by treatment using Nd:YAG laser.[106-108] There have also been cases in which favorable results could be obtained by treatment of anemia due to gastrointestinal bleeding[109] and of symptoms, such as airway obstruction, due to the mass effect of the lesion.[110] While transient purpura and swelling after treatment are unavoidable, they often cure rapidly.[99] Modifications of the irradiation setting and method are necessary to obtain satisfactory results and avoid serious complications, such as peroneal neuropathy[100] and pigmentation and scar formation of the facial skin,[106, 108] and we must learn from the experience of experts.

Nd:YAG laser irradiation by inserting a fiber into the lesion under ultrasound guidance has begun to be applied as a treatment to avoid damage of important organs and nerves,[98-100] therapeutic experience using this technique has been accumulated, and detailed records and reports have been

presented. At present, the results have been satisfactory in terms of safety and efficacy, and standardization of the procedure is anticipated.

CQ9: Is sclerotherapy effective for VMs?

Recommendation:

Sclerotherapy for VMs is effective for alleviating symptoms and reducing the size of the lesion and is recommended.

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| Strength of recommendation | 2 (weak) |
| Evidence | D (very weak) |

Comments

VMs are lesions that used to be called cavernous hemangioma or intramuscular hemangioma and differ from infantile hemangioma. VMs pose problems, such as pain, swelling, and functional impairment, and have been treated conventionally by surgical resection. In Western countries, percutaneous sclerotherapy has a long history. In 1989, Yakes et al. reported ethanol sclerotherapy for VMs, and the treatment has since been performed worldwide. Recently, sclerotherapy, which is mildly invasive, permits functional and morphological preservation, and can be performed repeatedly, has become popular. However, as of 2016, sclerotherapy is not covered by medical insurance in Japan. In addition, there has been no randomized controlled trial (RCT) on the usefulness of sclerotherapy for VMs compared with surgery or placebo.

As a result of secondary screening, 76, 3, and 3 papers were extracted from PubMed, Cochrane, and JCRM, respectively. They include 3 semi-RCTs, but randomization and blinding were insufficient, and their quality as RCTs was low. Also, the theme evaluated by all these RCTs was

“comparison of sclerosing agents in sclerotherapy”, and none compared sclerotherapy with other treatments. Therefore, control groups related to this CQ were not established, and their contribution as a whole is weak. The other literature was all case reports or case series, and the evidence level is D (very weak). As mentioned above, while the evidence level is low, most of the studies reported alleviation of symptoms and regression of lesions in a high percentage (70-90%) of the patients, suggesting the usefulness of sclerotherapy.

The sclerosing agents used included absolute ethanol, polidocanol, ethanolamine oleate, sodium tetradecyl sulfate (STS), and bleomycin. Polidocanol is approved as a sclerosing agent for lower limb varices and esophageal varices, and ethanolamine oleate as a sclerosing agent for esophageal varices. STS is not marketed in Japan. Each sclerosing agent has characteristic complications. Recently, injection of polidocanol, STS, etc., foamed by mixing with CO2 or air has been increasingly accepted. Sclerotherapy using ethanol is often performed under general anesthesia, but sclerotherapy using polidocanol or ethanolamine oleate can be performed under local anesthesia.

Three RCTs have been reported as studies that evaluated differences in therapeutic effect according to the sclerosing agent. However, randomization and blinding are insufficient, and their quality as an RCT is low. In addition, the theme evaluated in these RCTs was “comparison of sclerosing agents in sclerotherapy” rather than comparison with other treatments.

Although the evidence level is low, there have been a few case series that reported the usefulness of sclerotherapy, and a wide variety of sclerosing agents including ethanol, polidocanol, ethanolamine oleate, STS, and bleomycin were used. Among studies with a relatively large number of patients, there is a report that sclerotherapy using ethanol in 87 patients with craniofacial VMs resulted in a ≥75% decrease in size in 23 (32%) and a 25-75% decrease in size in 37 (52%).[111] The results of sclerotherapy using polidocanol in 50 patients with VMs were excellent in 19, good in 16, moderate improvement in 13, and unchanged or worse in 2.[92] The results of sclerotherapy using

ethanolamine oleate performed in 83 patients, who were mostly children, were complete remission of symptoms in 79 lesions and significant alleviation in 6 lesions.[112] Sclerotherapy using STS resulted in subjective improvements in 174 (85.3%) of 204 patients.[113] The results of sclerotherapy using bleomycin were complete cure in 185 of 260 patients, marked improvement in 44, and some improvement or no change in 31.[114] In addition, regarding the size of the lesion, a very satisfactory decrease was achieved in 104, and a satisfactory decrease was achieved in 10, of 120 patients.[115]

Papers that evaluated the types of VMs that are likely to respond to sclerotherapy include those by Goyal et al.,[116] Yun et al.,[117] Mimura et al.,[91] Rautio et al.,[118] Lee et al.,[111] Yamaki et al.,[119] and Nagao et al.[120] Types of lesions that were likely to be sclerosed were reported to be well-defined small (≤5 cm) lesions by Goyal et al.,[116] females, lesions showing no or delayed delineation of the draining vein, and lesions well-defined on MRI by Yun et al.,[117] small lesions, well-defined lesions, and lesions that show prolonged drug retention by Mimura et al.,[91] localized lesions by Lee et al.[111] and Yamaki et al.,[119] and slow flow type lesions by Nagao et al.[120] Nomura et al. evaluated the therapeutic effect according to the degrees of functional and gross improvements and reported that the therapeutic effect was greater in head and neck and trunk lesions than in the upper or lower limb lesions.[121] Moreover, Rautio et al. reported that the treatment-related improvement in QOL was higher when the lesion did not involve the muscle or was ≤5 cm in size.[118]

A wide variety of complications ranging from mild complications, such as transient neuropathy and local inflammation, to serious ones, such as myopathy, skin necrosis, and deep venous thrombosis/pulmonary embolism, have been reported. In sclerotherapy using ethanol or polidocanol, particularly serious life-threatening complications have been reported. Qiu et al. reviewed the literature concerning sclerotherapy for VMs and reported that shock and pulmonary embolism occurred in 0.19% each of 522 patients who underwent sclerotherapy using ethanol and that ethanol was used at 1 mL/kg in those who developed shock. He also reported that a decrease in

blood pressure/bradycardia was noted in 0.61% of 163 patients who underwent sclerotherapy using polidocanol but that its differentiation from vagus nerve reflex was clinically difficult.[122] Wong et al. reported a case that suffered shock after sclerotherapy using 0.86 g/kg ethanol but could be saved.[123] Tachibana et al. reported that 2 (1.1%) developed pulmonary embolism and that the amounts of ethanol used were 0.71 and 0.16 mL/kg.[124] Concerning sclerotherapy using polidocanol, also, children who suffered cardiac arrest have been reported by authors including Marrocco-Trischitta et al.[125] and Shimo et al.,[126] who used 4 mL of 1% polidocanol (body weight: 20 kg) and 10 mL of 3% polidocanol (15.6 kg), respectively.

In conclusion, sclerotherapy is generally considered effective for VMs, but its problems are that the evidence level is low and that the procedure has not been standardized. In addition, serious complications that are rare but life-threatening have been reported, and caution is needed in deciding the dose of the sclerosing agent.

CQ10: Are clotting abnormalities due to VMs an indication for radiotherapy?

Recommendation:

Radiotherapy should not be performed without careful evaluation because malignant neoplasm, growth disorders, and functional impairment have been reported as late complications.

Many reports included both VMs and vascular tumors in the subjects, which make it difficult to assess the therapeutic effects of radiotherapy.

| | |
|---|---|
| Strength of recommendation | 2 (weak) |
| Evidence | D (very weak) |

Comments

As a result of primary screening, 6 and 2 documents were retrieved from PubMed and JCRM. However, as a result of secondary screening, liver hemangioma was excluded, and 10 papers including the references from the previous guideline were reviewed. The reviewed papers were case series or case reports, and the evidence level of the literature as a whole is D “very weak”.

While there have been reports that radiotherapy was performed for the treatment of vascular tumors and vascular malformations, it is difficult to judge whether or not the treatment was performed by distinguishing the disorders.

According to many reports, radiotherapy has been performed to treat Kasabach-Merritt phenomenon.[127-131] On the contrary, while there is no mention about Kasabach-Merritt phenomenon, there is a report of 5 cases in which giant hemangiomas accompanied by clotting disorders, thrombocytopenia, heart failure, and bleeding could be controlled by multidisciplinary treatment including radiotherapy.[132]

However, vascular tumors that cause Kasabach-Merritt phenomenon are considered to be kaposiform hemangioendothelioma or tufted angioma rather than infantile hemangioma[133] (see CQ6, 30). Because VMs and infantile hemangiomas are mixed with other vascular tumors in the lesions described in these reports, and they are not considered to support implementation of radiotherapy for VMs and infantile hemangiomas.

Schild et al. reported 13 cases of symptomatic hemangioma (11 of which were pathologically diagnosed as cavernous hemangioma, but as the report is old, vascular tumors and vascular malformations were not distinguished and were probably mixed).[127] Radiotherapy at 6.25-40 Gy was carried out in these 13 cases. The lesions were located in the limbs in 5, face in 2, vertebral bodies in 3, pituitary fossa in 1, sacrum in 1, and bladder in 1. Note that organs that should be excluded in this CQ were included.

Of these cases, 2 (1 each with a limb and facial lesion) exhibited Kasabach-Merritt

phenomenon and showed normalization of clotting disorder (evaluated according to the platelet count and fibrinogen level) after treatment. However, these 2 cases were aged 3 years and 5 months, and the lesions may not have been VMs.

When the subjects were limited to patients with limb or facial lesions, CR was observed in 2, PR in 4, and no response in 1 in terms of decrease in the lesion size, and CR was observed in 4, PR in 1, and no response in 2 in terms of the control of symptoms.

A serious treatment-related complication, which was unilateral visual impairment, was noted in 1 (14 Gy/8 fr).[127]

These problems have been recognized as late complications of radiotherapy for vascular tumors or vascular malformations; malignant neoplasms, such as breast cancer,[134] thyroid cancer,[135] and vascular sarcoma,[136] visual impairment mentioned above,[127] shortening of the lower limb, and restriction of the joint motion range.[130]

According to Coldwell et al., late complications of radiotherapy for hemangiomas in infancy include bruise and Stewart-Treves syndrome after the patients reach adulthood. Angiosarcoma is also observed. They reported that the median survival period was 24 months, and the 5-year survival rate was about 10%, in those who developed angiosarcoma.[136]

As observed above, the diagnosis was not confirmed in the reports that have suggested the effectiveness of radiotherapy, and its indications have not been specified. In addition, there have been a considerable number of reports of late complications due to radiotherapy. Thus radiotherapy should not be performed without careful evaluation.

CQ11: Is there difference in the effectiveness of dye laser treatment for capillary malformations according to the site of the body?

Recommendation:

Dye laser treatment for capillary malformations is likely more effective in the face and neck region compared with other sites, and it is more likely to cause complications such as pigmentation in the limbs.

| | |
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| Strength of recommendation | 2 (weak) |
| Evidence | C (weak) |

Comments

As a result of literature searches, 176 papers consisting of 139 from PubMed and 37 from JCRM were extracted. They included a few reports that were allegedly RCTs but were not real RCTs. Therefore, a total of 26 papers consisting of 15 from PubMed and 11 from JCRM including case series with a large number (≥100) of relevant cases were selected by secondary screening. In addition, a total of 17 papers were adopted as references for the comments in the guidelines by adding 3 papers in English extracted by manual search to 6 from PubMed and 8 from JCRM considered to be relevant or closely related to the CQ among those selected by secondary screening. Since there was no RCT, the evidence as a whole was rated as C (weak).

Concerning the effect of dye laser treatment for capillary malformations, most of the reports were about the effects for hemangioma simplex or port-wine hemangioma in Japan and port-wine stain abroad.

There have been a few papers that evaluated the therapeutic results of dye laser treatment according to the site in a small to relatively large number of patients.[137-151] The laser equipment used varies from early dye laser to pulsed dye laser with adjustable pulse duration with a cooling system, and reports limited to variable-pulse pulsed-dye laser with a cooling system, which is widely used today, are extremely few.

According to many reports, the response rate is higher in the face and neck region than in the trunk and limbs.[137-148] In the face, it has been reported that the response rate is higher in the palpebral, forehead and temporal, and lateral buccal regions but is significantly lower in the territory of the 2nd division of the trigeminal nerve(dermatome V2), and that the number of irradiations tends to increase in the midline region, frequently resulting in persistence of redness.[149] There is a report that the response rate did not differ significantly among regions in the lower limb.[150] While the number of ~~subjects~~ patients was small, it has been reported that treatment of the foot involves stronger pain but was less effective than in the face but that the degree of patient satisfaction was relatively high.[151]

The incidence of complications of dye laser (bleb formation, depigmentation, pigmentation, scar formation, etc.) is reported to be low, being 1.7% in adults, 0.6% in children, and about 1.4% in all patients even when all sites of the body are included, and no significant difference has been reported in the age at the beginning of treatment, Fitzpatrick skin type,[152] site, number of treatments, or irradiation energy between those who developed complications and those who did not, but complications tend to occur more frequently in the lower limbs.[153] Moreover, there is a report that complications, such as pigmentation, depigmentation, and atrophic scar, were observed more frequently in the lower limbs.[151]

CQ12: Do capillary malformations recur after dye laser treatment?

Recommendation:

Although the effectiveness of dye laser treatment for capillary malformations is established, the recurrence rate may increase with time after treatment.

Strength of recommendation 2 (weak)

Evidence C (weak)

Comments

As a result of literature searches, a total of 211 papers consisting of 149 from PubMed, 53 from Cochrane, and 9 from JCRM were retrieved. They did not include RCTs, and a total of 30 papers consisting of 23 from PubMed and 7 from Cochrane, which were mostly case reports and case series studies, were extracted by secondary screening. In addition, a total of 10 papers that were relevant and closely related to the CQ (including 8 case series) consisting of 7 from PubMed, 2 from Cochrane, and 1 in English retrieved by manual search were adopted as references for the guidelines. Since there was no RCT, the strength of evidence of the group of literature concerning this CQ is C "weak".

Concerning papers that referred to "whether or not capillary malformations recur after dye laser treatment", there are 4 retrospective studies after treatment by pulsed dye laser (wavelength: 585 nm) with a cooling system, and the recurrence rate was 15.9-35%.[154-157] Also, there is a report that the recurrence rate increased with time after treatment and was 3.1% after 1 year, 20.8% after 2 years, 40% after 3 years, and 50% after 4 years.[154] Therefore, it is necessary to treat capillary malformations with the recurrence after dye laser treatment in mind.

It is difficult to strictly distinguish whether the recurrence is generation of new dilated vessels after laser therapy or it is regeneration of blood vessels damaged due to treatment or re-proliferation of remaining vessels. However, there have been reports that, in an experiment using mice, angiogenesis occurred in the process of wound healing at the site of irradiation in early recurrence[158] and that, in an experiment using hamsters, complete treatment was difficult, and morbid vessels persisted, because coagulation was difficult to induce by dye laser irradiation in vessels ≤2-16 μm in diameter.[159] While there is a report that genes affected by dye laser therapy early

after treatment could be identified,[160] further evaluation is necessary to clarify their relationships with the recurrence.

Concerning the prevention of recurrence, there is a report that the recurrence-free period was long in the patients treated with a variable-pulse pulsed-dye laser with a cooling system (wavelength: 595 nm), which is widely used today, and they were treated within 6 months after birth.[161] In addition, there have been reports of animal experiments using Rapamycin, which inhibits angiogenesis after laser irradiation,[158, 162] and of prospective RCT using imiquimod,[163, 164] and these treatments were considered effective for the prevention of recurrence. However, careful evaluation by large-scale investigations, including the assessment of the safety concerning drugs, is considered necessary.

CQ13: Is dye laser irradiation for capillary malformations more effective as it is initiated at a younger age?

Recommendation:

Laser therapy before the age of 1 year may be effective, and the earliest possible initiation of treatment is recommended as an option.

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| Strength of recommendation | 2 (weak) |
| Evidence | D (very weak) |

Comments

Concerning the timing of treatment for capillary malformations, there is the opinion that early initiation of treatment is recommended, because, in young children, the skin is thinner, so the depth of penetration is larger, the vascular wall is also immature, cure after laser irradiation is better,

pigmentation is less, and the irradiation area is small, so the treatment efficiency is higher. However, there is still controversy. As a result of secondary screening of past reports, 6 and 1 were extracted from PubMed and JCRM, respectively. While the papers selected by these screening procedures include 2 papers on prospective studies as described below, their conclusions differed, and the evidence level is considered to decline when these references are reviewed together.

Oguri et al. performed a non-randomized controlled trial by dividing children into those aged 0-12 months, 13-24 months, and 25-36 months and observed significant differences in the response rate combining ‘markedly effective’ and ‘effective’ among the groups. They also compared the response rate according to the age in months at the beginning of treatment in the 0-year-old group and reported that the response rate was higher as the treatment was initiated ealier.[137] Furthermore, Nguyen et al. divided their patients into those aged less than 1 year, those aged 1-6 years, and those aged 6 or more years and investigated the correlation between treatment response and age. They reported that those aged less than 1 year and lesions with a size of less than 20 $cm^2$ located in the center of the face showed the best treatment response.[165]

Among reports suggesting no difference in the therapeutic effect according to the age at the beginning of treatment, van der Horst et al. studied 100 patients with untreated capillary malformations of the head and neck region prospectively and concluded from the results of colorimetry and clinical evaluation that there was no significant difference in the therapeutic effect of pulsed dye laser among the 4 groups in which the treatment was started at the age of 0-5, 6-11, 12-17, and 18-31 years.[166] In the retrospective study of Katugampola et al., also, comparison of 4 groups in which treatment was started at the age of 0-5, 6-12, 13-50, and 50+ years showed no significant difference in the therapeutic effect.[139]

Among the above reports, those did not affirm the usefulness of early laser treatment were relatively old. Also, reports of Oguri et al.[137] and Nguyen et al.[165] indicated laser therapy may be

more effective in those aged less than 1 year. In addition, the effectiveness of laser clearly declines when the lesion is elevated or thickens with time. In consideration of “benefits” of early laser treatment and “harms”, which include the occasional necessity of general anesthesia for laser treatment around the eye in small children, the recommendation level was rated as 2D based on the consensus of this guideline drafting committee.

CQ14: Is propranolol safe and effective for infantile hemangiomas?

Recommendation:

If administered under careful monitoring, oral propranolol therapy may be the first choice for the treatment of infantile hemangioma.

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|---|---|
| Strength of recommendation | 1 (strong) |
| Evidence | A (strong) |

Comments

1) Effectiveness; There was the serendipity that regression of hemangioma was induced in a child under steroid therapy with a giant infantile hemangioma by propranolol administered for obstructive hypertrophic cardiomyopathy in 2008.[167] Based on this report, oral propranolol therapy began to be utilized for the treatment of infantile hemangioma, and its high efficacy against alarming hemangioma/life-threatening hemangioma in the proliferating phase and in patients with cosmetic problems, such as giant lesions in the face, those with ulcerated and hemorrhagic lesions, and those who may develop functional impairment, has been demonstrated, resulting in its use (Hemangiol) as the first choice in Western countries. In addition, its effectiveness for the treatment of hemangiomas after the proliferating phase was also described. Moreover, a group of physicians uses propranolol

earlier due to cosmetic significance and at the request of the family even in cases of small or localized lesions, and it is also effective in such cases.

A total of 131 papers consisting of 25 from JCRM, 106 from PubMed, and 0 from Cochrane Library were extracted as related to the CQ, "Is propranolol safe and effective for infantile hemangioma?", and they were subjected to primary and secondary screenings with reduction of hemangioma (effectiveness of propranolol) and treatment-related complications (adverse effects) as outcomes. Twenty-six papers, most of which were RCTs or observational studies, were adopted.[168-193]

For example, Hogeling et al. administered placebo or propranolol at 2 mg/kg/day for 6 months with randomization to 40 patients aged 9 weeks-5 years with infantile hemangiomas in the face or sites with the potential for disfigurement. They reported significant improvements in size, redness, and elevation in the propranolol group. Elevated lesions disappeared in 4 of the 19 patients in the propranolol group but none of the 18 patients in the placebo group. As for adverse events, the trial was interrupted in 1 patient due to upper respiratory tract infection, and conditions including bronchiolitis, gastroenteritis, streptococcal infection, cool extremities, dental caries, and sleep disturbance were observed.[179]

Zaher et al. observed 45 patients by randomly dividing them into 15 each treated by oral administration, topical application, and intralesional injection of propranolol. Responses were observed in 60% in the oral group, 20% in the topical ointment group, and 13.3% in the injection group. No major adverse events were noted, and the trial was discontinued in 1 in the oral group and 3 in the injection group due to inconvenience or pain of the treatment.[180]

Malik et al. randomly allotted 30 patients aged 1 week-8 months to propranolol alone, prednisolone alone, or both propranolol and prednisolone. The authors found that mean initial response time were lower in the propranolol group than in the prednisolone group but that there was

no clear difference between the propranolol + prednisolone group and propranolol alone group.[181] All 10 patients in the propranolol group and 9 patients in the corticosteroid group responded to the 3-month treatment. However, adverse events were observed in 2 of the 10 patients in the propranolol group (asymptomatic hypoglycemia, insomnia) but 9 of the 10 patients in the steroid group (cushingoid appearance, gastrointestinal upset, etc.), and were more frequently in the latter group.

Bauman performed a phase 2, investigator-blinded, multi-center RCT in 44 patients aged 2 weeks-6 months. Propranolol or prednisolone (2 mg/kg/day) was administered orally until halted owing to toxic effects or clinical response. During 4-months treatment, no significant difference was observed between the two groups, for example, with regression of 5 of the 6 tumors in the corticosteroid group and 9 of the 10 tumors in the propranolol group. For long-term analyses, the effect of prednisolone appeared earlier. While the incidence of adverse events as a whole did not differ between the two groups, severe adverse events were observed in 1 of the 11 patients in the propranolol group but 5 of the 7 patients in the prednisolone group, significantly more frequently in the latter group.[182]

Léauté-Labrèze et al. carried out an RCT in patients aged less than 4 months by comparing 7 administered and 7 not administered propranolol. Since color change and softening were observed within 24 hours, and the thickness and size of the lesions decreased within 4 weeks in the propranolol group, the treatment was considered useful for the prevention of scarring. No serious adverse effect was observed except asymptomatic mild decrease in heart rate and diastolic blood pressure.[183]

There have also been comparisons between atenolol and propranolol and between laser and laser plus topical propranolol.[184, 185] In 2015, the largest RCT was published in the New England Journal of Medicine, also reporting that propranolol was significantly effective for hemangioma

compared with placebo.[186] Hemangioma showed complete or nearly complete resolution after 6-month treatment in 2 (4%) of 55 patients in the placebo group and 61 (60%) of 101 patients in the 3 mg/kg/day propranolol group.

Furthermore, there have also been a few systematic reviews and meta-analyses primarily of observational studies. Menezes et al. reviewed 49 English papers published between June 2008 and September 2010, and summarized 6 studies with 10 or more patients administered propranolol (totally 154 patients). Propranolol was administered to infants with a mean age of 4.5 months at a dose of 2 mg/kg/day in 65% and 3 mg/kg/day in 25.3%. Two-thirds of the patients were treated with propranolol alone. Recurrence was observed in 21% after treatment for a mean of 4.3 months, and adverse events including hypotension, somnolence, wheezing, insomnia, agitation, nightmare, cool hands, night sweat, gastroesophageal reflux disease, and psoriasiform rash appeared in 18.1%.[187]

Marqueling et al. reviewed the therapeutic results in 1,264 patients (including 806 girls) in 41 reports published from 2008 to 2012 retrieved from Medline and Cochrane database. The treatment was initiated at a mean age of 6.6 months at 2.1 mg/kg/day and continued for a mean of 6.4 months. The overall response rate was 98%, and the treatment was also effective in clinically problematic areas such as the face (100%), airway (100%), periorbital (98%), head and neck region (97%), and parotid gland (82%). However, recurrence was observed in 17% after treatment. Adverse effects were noted in 371 of 1,189 patients. Change in sleep (136 patients) and acrocyanosis (61) were the most frequent among them, and hypotension was observed in 44, bradycardia in 9, and hypoglycemia in 4 as serious complications. In conclusion, the grade of recommendation was 1, quality of evidence is A, and propranolol was recommended as the first-line drug for complicated infantile hemangiomas. Regarding adverse effects, the grade of recommendation was 1, quality of evidence was A or B. while serious adverse effects may be observed, their frequency is low, and they can be usually avoided by proper monitoring at initiation of treatment.[188]

Xu et al., on the other hand, evaluated volume change, improvement in overall appearance, visual function, and adverse effects using 15 online databases. The data of 419 cases were analyzed, but meta-analysis was not performed because of the wide differences among studies. Some studies showed superiority of propranolol compared with corticosteroid in reducing volume and improving the overall appearance. No marked difference was noted in adverse effects or visual function.[189]

In addition, in meta-analysis of 16 studies (2,629 cases) and 25 studies (795) published in 1965-2012, 69% of the patients responded to 12-month corticosteroid therapy, but the response rate to propranolol was 97% with a significant difference.[190]

In periorbital hemangiomas, the response rate to propranolol was shown to be significantly higher than that to corticosteroid by meta-analysis of papers published before 2013,[191] and propranolol showed the strongest effect against airway hemangiomas compared with steroid, $CO_2$ laser, and vincristine on meta-analysis.[192, 193]

From these observations, we concluded that propranolol was significantly more effective than placebo and to be similarly effective compared with corticosteroid. Concerning the safety, propranolol is considered to have significantly fewer adverse effects than corticosteroid. Since there have been multiple RCTs and systematic reviews or meta-analyses directly related to this CQ, the evidence level is considered to be extremely high.

2) Meta-analysis: Regarding the effectiveness and adverse effects of propranolol, a large number of systematic reviews and meta-analyses based on observational studies are already present in the above 26 papers. We, therefore, used only 4 reports on interventional studies for meta-analysis.[179, 181, 182, 186]

As a result of meta-analysis, regarding “tumor reduction”, it was found that propranolol had significantly stronger reducing effects than placebo and that it had a stronger reducing effect, which,

however, was not significant, compared with corticosteroid. Concerning “complications”, propranolol was compared with steroid and was shown by 2 RCTs to have significantly fewer adverse events compared with corticosteroid. Since this meta-analysis showed statistical significance in stronger reducing effect of propranolol compared with placebo and in fewer complications compared with steroid, and since our results were similar to those of systematic reviews of many existing observational studies considered to have high-quality evidence, we supposed that there was a major tendency in this CQ and judged the evidence level as A.

3) Estimated action mechanism; Beta-blockers have a wide range of actions on the blood vessels and vascular endothelium, and have diverse actions on cell proliferation and vascular remodeling. Thus, the action mechanism of propranolol on infantile hemangiomas is still unclear. In vascular endothelial cells, propranolol is considered to induce vascular contraction by suppressing NO production, inhibit renin production, control angiogenesis by regulating the expression of VEGF•bFGF•MMP2/MMP9, and induce apoptosis, but it may also affect pericytes and hemangioma stem cells.[194-196]

4) Adverse events associated with propranolol in children

In conducting propranolol therapy, it is necessary to have knowledge about possible adverse effects, their symptoms, and their management. In addition, as there are also preventive measures for, and points of attention about, adverse effects and the timing for discontinuation of propranolol, sufficient explanation to the patients and their families is essential.

Adverse events that have been reported include sleep disorders, peripheral cyanosis, hypotension (symptomatic, asymptomatic), bradycardia (symptomatic, asymptomatic), hypoglycemia, respiratory disorders, gastrointestinal disorders, and mental disorders. Severe cases

that require interruption of treatment are few, but particular caution is needed regarding the following points.[188, 195-199]

a) Since there is the risk of hypoglycemia, the patient should be fed before and after propranolol administration. If the patient cannot be fed, or is vomiting, for some reason, the administration should be suspended.

b) Since propranolol has cardiovascular adverse effects, such as hypotension and bradycardia, interviewing for the past history and familial history, examination, and electrocardiogram are recommended before treatment. Even if no abnormality is noted on these examinations, hypotension, bradycardia, etc., may occur during treatment. In such cases, interruption of the administration is necessary.

c) Propranolol is contraindicated for bronchial asthma as it causes bronchial contraction due to its β2-blocking action. Caution is also necessary in patients who have been suspected to have bronchial asthma.

CQ15: What are effective treatments for ulcer formation in infantile hemangioma?

(1) Propranolol

Recommendation:

The administration of propranolol is recommended for ulcer formation.

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| Strength of recommendation | 2 (weak) |
| Evidence | C (weak) |

(2) Topical administration of antibiotics

Recommendation:

Topical and systemic administration of antibiotics is recommended for ulcer formation.

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| Strength of recommendation | 2 (weak) |
| Evidence | D (very weak) |

(3) Dressings

Recommendation:

The use of dressings is recommended for ulcer formation.

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| Strength of recommendation | 2 (weak) |
| Evidence | D (very weak) |

(4) Laser therapy

Recommendation:

Although laser therapy may be effective in some patients with ulcer formation, the evidence is not considered sufficient at present.

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| Strength of recommendation | 2 (weak) |
| Evidence | D (very weak) |

(5) Systemic administration of steroid

Recommendation:

Systemic administration of steroid is recommended not to be performed for ulcer formation.

Strength of recommendation 2 (weak)

Evidence D (very weak)

(6) Platelet-derived growth factor preparations

Recommendation:

The accumulation of cases is insufficient for the judgment of the recommendability of the use of platelet-derived growth factor preparations for ulcer formation.

Strength of recommendation No recommendation

Evidence D (very weak)

Comments

Concerning this CQ, 42 papers in Japanese and 156 in English were retrieved. As a result of their primary screening, 47 papers were submitted to secondary screening for this CQ. None of them were about studies with a high level of evidence, such as RCT, and they were all retrospective studies, case series, or case reports.

As a result, 15 papers in English were adopted, and the evidence level was C for propranolol alone, because of the presence of a prospective controlled trial, but D for other treatments, because the related papers were case reports or case series.

According to cross-sectional analysis in a multicenter prospective cohort study in 1,096 cases of infantile hemangioma by Chamlin et al.,[200] it was complicated by ulcer, which was or was not bleeding, in 173 (15.8%), the median age of the patients was 4.0 months (SD = 8.5, mean = 6.6 months), and the age at the first examination was significantly lower in patients with ulcerated hemangioma (median = 3.5 months, mean = 3.98 months) than in those with non-ulcerated

hemangioma.

By the site, ulcer formation was observed in 21 (30%) of 71 patients in the lower lip, 25 (25%) of 100 patients in the neck, and 46 (50%) of 93 patients in the perianal/perigenital area, and the frequency was statistically lowest in the upper eyelid ($p = 0.0140$).

Ulcer formation was observed more frequently in mixed or segmental hemangiomas. Bleeding was noted in 78 lesions (41%) and was mild in 56 (29%), moderate in 11 (6%), and severe in 4 (2%). Severe bleeding occurred in 3 lesions in the limbs and 1 lesion in the face, and bleeding occurred in 2 cases at home. Two cases required blood transfusion by hospitalization, because they showed symptoms due to serious bleeding. Of the ulcerated hemangiomas, 67 (35%) were in the proliferating phase.

Ulcerated hemangiomas required treatment (odds ratio (OR) = 6.86, 95% CI = 3.70-12.71, $p <0.0001$), and non-ulcerated hemangiomas were observed (OR = 19.01, 95% CI = 11.23-28.88, $p <0.0001$). Ulcerated hemangiomas tended to be treated by conventional wound care and pulsed dye lase (OR = 2.03, 95% CI = 1.19-3.46, $p <0.0091$), and non-ulcerated hemangiomas were treated by topical glucocorticoid administration (OR = 2.57, 95% CI = 1.49-4.43, $p <0.0007$) and surgical resection (OR = 2.04, 95% CI = 1.08-3.86, $p <0.0286$).

However, propranolol has recently been suggested to be effective regardless of the presence or absence of ulcer formation, and as it has few adverse effects, it is expected to become the first choice treatment in the future.

[Treatments]

(1) Oral propranolol

Hermans et al. treated 20 previously treated patients with ulcerated infantile hemangioma using propranolol and compared them with 36 patients treated without propranolol.[171] The

administration was initiated by hospitalization, and the dose was increased from 0.7-1.0 to 2.0-2.5 mg/kg/day in 3 divided doses at an interval of at least 3 days. The blood pressure, heart rate, and blood sugar level were monitored during the initial administration period, and the administration was continued on an outpatient basis until the age of 1 year. The mean age at the beginning of propranolol administration was 3.5 months, and the mean duration of administration was 9.1 months. Not only the color and elevation of the lesion but also pain was reduced from early after the beginning of administration. The administration was concluded before the age of 1 year in 19 patients, and no recurrence of ulcer was noted in any of these patients except that some reactivation (enlargement) of hemangioma was observed after the discontinuation in 4 of these patients.

The mean time until complete cure of ulcer was 8.7 weeks, and those in whom the administration was initiated later (>3.5 months) tended to require a longer time until cure than those in whom the administration was initiated earlier ($p = 0.025$). Also, analysis using the t-test showed a significant difference in the time until disappearance of the tumor, which was 8.7 and 22.4 weeks ($t = 2.6$, $df = 38$, $p = 0.012$, 95% CI = 3.2-24.2) in the treated and control groups, respectively. Temporary sleepiness/malaise was observed in 6 patients, grizzling before falling asleep in 2 patients, coldness of the limbs in 6 patients, anorexia in 2 patients, and gastrointestinal disorders (diarrhea, vomiting) in 1 patient, but no adverse event was noted in 9 patients.

Vercellino et al.[201] (started the administration at 1 mg/kg/day and increased to 2 mg/kg/day) and Sadykov et al.[202] (started the administration at 2 mg/kg/day) also reported that propranolol was effective.

2) Topical and/or systemic administration of antibiotics

Kim et al. externally administered antibiotics in 40 patients with ulcerated hemangioma and reported that the results were better in 37 patients (92.5%), worse in 0 patient, and no change in 3

patients (7.5%). They also systemically administered antibiotics in 26 patients and reported that the results were better in 24 patients (92.3%), worse in 2 patients (7.7%), and no change in 0 patient.[203]

Wananukul et al. externally and/or systemically administered antibiotics in 41 patients with ulcerated hemangioma and reported improvement in 19 patients (46%).[204]

Pandey et al. treated 608 patients showing ulcer formation with an ointment containing an antibiotic (mupirocin, sodium fusidate, sisomicin, or metronidazole) combined with systemic administration of an antibiotic (amoxiclav at 20-40 mg/kg/day) in those with ulcers with an area of >10 $cm^2$ and examined the effectiveness of treatment according to the time until cure. The time until cure was 32.63 ± 13.06 days in superficial lesions, 42.89 ± 19.89 days in mixed lesions, and 57.03 ± 16.12 days in extensive lesions, with a mean of 40.09 ± 19.41 days in all lesions combined, showing significant differences among the 3 groups ($p < 0.05$). They also reported that the time until cure was significantly longer in larger (>10 $cm^2$) than smaller ulcers ($p < 0.05$).[205]

(3) Dressings

Kim et al. treated 25 patients using dressings and reported that the results were better in 23 patients (92%), worse in 0 patient, and no change in 2 patients (8%).[203] Oranje et al. applied polyurethane film and reported rapid relief of pain and cure of ulcer in 1-2 months.[206] In addition, Bauland et al. treated 41 patients using a non-adhering dressing containing an antibiotic and reported that the results were good in 26 patients (63.4%), moderate in 5 patients (12.2%), and little change in 10 patients (24.4%).[207]

(4) Laser therapy

In the 1980s-1990s, there were reports of argon, NdYAG, KTP, etc., but recent reports are primarily about treatment using dye laser.[208-211] Morelli et al. treated 37 patients with ulcerated

hemangioma by dye laser irradiation (SPTL1b®, Syneron Candela, wavelength: 585 nm, spot size: 5-7 mm, irradiation power: 5-6.8 J/cm$^2$, pulse width: 0.45 msec) and reported that the number of irradiations until cure was once in 26 patients (68%) and twice in 8 patients (21%) and that the mean period from the first treatment until cure of ulcer was 2.84 ± 0.22 weeks.[208] Lacour et al. irradiated 8 patients with ulcerated hemangioma that resisted conventional treatments using the same equipment and reported acceleration of cure.[209] David et al. performed dye laser irradiation (Cynosure, PhotoGenica V®, wavelength: 585 nm, spot size: 5-7 mm, irradiation power: 5-6.8 J/cm$^2$, pulse width: 0.3-0.5 msec) in 78 patients and reported the effectiveness of laser therapy alone in 72 (92.3%).[210] Also, Michel performed 1 or 2 irradiations using Dermobeam 2000® with a cooling system 595 nm (2 pulsed irradiations with a 10% overlap, spot size: 7 mm, irradiation power: 4-8 J/cm$^2$) and reported resolution of pain in 10 of the 12 patients.[211] Moreover, Di Maio et al. performed laser treatment in 65 patients with hemangioma with ulcer and reported that the effect was excellent and that no clear adverse events were observed, because scarring, which was noted in a few patients, did not differ markedly compared with scarring that occurs after conventional treatments.[212]

However, Kim et al. treated 22 patients with pulsed dye laser and reported that the results were better in 11 patients (50%), worse in 1 patient (4.5%), and no change in 4 patients (18.2%), but warned that 5 patients in the proliferating phase showed ulcer formation after irradiation.[203]

As observed above, although there have been multiple reports of the effectiveness of laser therapy against ulcer as factors of “benefit”, many reports are relatively old and lack controls, and the evidence is not considered sufficient. Further accumulation of cases is necessary. Laser may be effective in limited patients, but as there is the risk of ulcer formation as an adverse effect of laser irradiation of infantile non-ulcerated hemangioma, greater caution is needed in treating already ulcerated lesions.

(5) Steroids

There have been few reports on steroid therapy focusing on ulcer. Kim et al. treated 7 patients by local steroid injections and reported that the results were better in 4 patients (57.1%), worse in 1 patient (14.3%), and no change in 1 patient (14.3%). They also systemically administered steroid to 22 patients and reported that the results were better in 16 patients (72.7%), worse in 1 patient (4.5%), and no change in 5 patients (22.7%). Based on these results, they considered that the treatment was effective for reducing the lesion size, and there are few other reports suggesting the effectiveness of steroid.[203] Considering that the patients are infants and that there are other treatment options, steroid cannot be recommended at present.

(6) External preparations of recombinant human platelet-derived growth factor

0.01% becaplermin (Regranex®) is a preparation for diabetic foot ulcer approved by the FDA in 1997. Sugarman et al.[213] and Metz et al.[214] reported its effectiveness for the treatment of ulcerated hemangioma in 1 and 8 patients, respectively, but its effectiveness cannot be appraised at present because of the deficiency of cases.

CQ16: Is intralesional corticosteroid injection more effective than systemic administration for infantile hemangioma?

Recommendation:

Treatment using corticosteroid is effective for inducing early regression of hemangioma. While no significant difference is observed in the effectiveness between intralesional injection and systemic administration, attention to complications including those at the administration site, such as the periocular region, on local injection and those, such as hypertension and growth retardation, on systemic administration is necessary.

| | |
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| Strength of recommendation | 2 (wean) |
| Evidence | B (moderate) |

Comments

As a result of primary screening, 99, 9, and 35 papers were extracted from PubMed, Cochrane, and JCRM, respectively, and 4 papers in English were subjected to secondary screening for this CQ. There was 1 report of an RCT, but the other reports were about case series while they evaluated a large number of cases. In addition, 2 papers on complications considered important in relation to intralesional corticosteroid injection for periocular lesions were added by manual search. Since there is a report of an RCT, and since other case series studies with a large number of subjects presented the results that there was no significant difference in the effectiveness of corticosteroid depending on the administration method, the strength of evidence was rated as “B”.

There was 1 report of an RCT focusing on “Is intralesional corticosteroid injection more effective than systemic administration for infantile hemangioma?”.[215] In this trial, the subjects were divided into control, oral administration (prednisolone at 2 mg/kg/day every other day for 6 weeks), and intralesional injection (triamcinolone at 1-5 mg/kg with a maximum of 30 mg once a month for 6 months) groups, and the lesion size was significantly reduced in the treated groups compared with the control group. While no significant difference was noted between the oral administration and the intralesional injection groups, the reduction rate tended to be larger in the local injection group, and local injection was concluded to be slightly superior.[215]

There were reports of case series with more than 1,000 subjects, but the findings were not statistically analyzed.[216, 217] Although both intralesional injection and oral administration were effective, there was also a mixed group of intralesional injection and oral administration, the

condition of patients varied among the 3 groups (intralesional injection, oral administration, mixed), and the effectiveness according to the administration method was not shown. Regarding complications, systemic symptoms, such as hypertension, retarded body weight gains, and cushingoid appearance, were reported to be more frequent on oral administration than intralesional injection.[216, 217] Moreover, concerning complications, in one report, periocular lesions were excluded from the targets of intralesional injection to avoid its effect on visual function.[218] Actually, there have also been case reports that visual impairment was caused by occlusion of the retinal artery after intralesional corticosteroid injection for periocular hemangiomas.[219, 220] Currently, in Japan, intralesional corticosteroid injection is a treatment unapproved by the national health insurance system.

CQ17: Is topical therapy effective for infantile hemangioma?

Recommendation:

Although it must be noted that there are no reports of comparison with placebo and that the degree of improvement is smaller compared with systemically administered drugs, external medication can be an option for the treatment of infantile hemangioma with no risk of complications if drugs with milder adverse effects are selected.

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| Strength of recommendation | 2 (weak) |
| Evidence | C (weak) |

Comments

As a result of literature searches, a total of 111 papers consisting of 70, 7, and 34 papers from PubMed, Cochrane, and JCRM, respectively, were extracted. They included 1 RCT study.

Including this RCT, 48 papers were extracted by secondary screening. In addition to the papers selected by secondary screening as closely related to the CQ, a total of 47 papers obtained by manual search were adopted as reference for the preparation of guidelines. There was 1 RCT, and comparative studies of therapeutic results by topical therapy and case series studies with a relatively large number of subjects were adopted as papers of relatively high quality, the strength of evidence was rated as C “weak”.

In the reports related to the CQ:

1) Drug type The drugs were classified into imiquimod, timolol, propranolol, corticosteroid, and others.[214, 221-224]

2) Drug concentration and dosage form Imiquimod was used as a 5% cream,[221, 225-232] timolol as 0.5% ophthalmic solution or gel,[221, 222, 231, 233-242] propranolol as 1% ointment,[180, 233, 240, 243, 244] and corticosteroid were often used as ointments of agents ranked as relatively strong such as clobetasol propionate, halobetasol propionate, and betamethasone dipropionate.[245, 246]

3) Methods for external application Frequent administration methods were once a day every other day for imiquimod, 2 times a day every day at 1-2 drops each time for timolol, 2 times a day every day for propranolol, and 2 times a day every day for corticosteroid.

4) Methods for efficacy evaluation Comparison of gross findings and photographs were adopted in all papers. The area was compared using photographs in one report.[226] There was also a report of half-side test for a control.[227]

5) Adverse effects No systemic adverse effect was reported, and most adverse effects were local. Imiquimod caused pain, flare, and erosion relatively frequently.[230, 232] Few local adverse effects were reported for timolol and propranolol.[231, 233, 240, 241, 244] No local adverse effects were reported also by corticosteroid.[245, 246]

6) Relative advantages of drugs　Imiquimod has been reported to have usefulness comparable to that of external beta blockers, but it is not considered superior in terms of adverse effects.[225, 227, 229, 231]

Corticosteroid was not shown to be superior in efficacy compared with beta blockers.

There was also one RCT study concerning the CQ,[180] which is related to the topical propranolol concerning drugs. In this RCT, 15 each of a total of 45 subjects were allotted to oral (propranolol at 2 mg/kg/day, 2 times a day), topical (1% propranolol water soluble ointment, applied 2 times a day), and local injection (1 mg/1 mL, 0.2 mL/1 cm in diameter, 1 mL/injection at the maximum, 1 time/week) groups. Ten patients (66.7%) in the topical group responded, but they were fewer than 13 (86.7%) in the oral group. The time until the appearance of the effect and time until complete cure were also longer in the topical group than in the oral group. Concerning complications, none was observed in the topical group, but 1 patient in the oral group showed unexplained syncope as an adverse effect and was excluded. While decreases in the heart rate and blood pressure were observed in 3 in the oral group, they did not necessitate interruption of the study. In the local injection group, 8 (53.3%) responded, but 3 were lost due to pain and trouble. From these results, the study concluded that topical therapy is an option to be evaluated for patients with a risk of adverse reactions to oral medication. While there were no reports of comparison under the same conditions, comparative studies of therapeutic results by topical therapy and case series studies with a relatively large number were adopted as relatively high-quality papers. In all these reports, topical therapy of beta blockers (propranolol, timolol) was effective to an extent with no serious complications.

Thus, topical therapy, particularly, of beta blockers is considered generally useful, but there has not been a report of its comparison with placebo, and further accumulation of cases is necessary.

Research by comparison between dye laser treatment and topical beta blocker therapy is

considered to be necessary.

CQ18: Is compression therapy effective for infantile hemangioma?

Recommendation:

Although appropriate compression method must be selected for individual patients, compression therapy may be regarded as an option on condition that the therapy is carried out by a skilled physician. Sufficient attention to skin abnormalities and local/neighboring growth disturbance due to the compression are needed.

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| Strength of recommendation | 2 (weak) |
| Evidence | D (very weak) |

Comments

While 23, 1, and 14 papers were extracted from PubMed, Cochrane, and JCRM, respectively, only 3 case reports remained to be reviewed as a result of 1st and 2nd screening. Thus, the evidence level is very low at D (very weak).

According to a case report of ulcerated infantile hemangiomas of the limbs by Kaplan et al.,[247] the ulcers of most patients showed rapid improvements and cured within 2 weeks by compression therapy using the self-adherent wrap Coban (3M CO.) combined with topical treatment with an antibiotic ointment (or early systemic antibiotic administration when secondary infection was apparent). They concluded that, compared with antibiotic ointment alone, its combination with compression therapy was more effective, and is a safe and easy treatment that promotes regression of hemangiomas.

Ochi et al. reported 12 cases of infantile hemangioma (9 girls and 3 boys with a mean age of

8.4 months; sites of the lesion: limbs in 6, head and neck in 5, and trunk in 1). By treatment using elastic bandages (5 patients), Presnet (4), supporter (1), or Elatex and cryotherapy (2), the hemangiomas disappeared or decreased in size in 11 of the 12 patients, with only 1 (head and neck) showing no improvement. The time until the disappearance of the lesion in the 11 responders was 2 months to 3 years (mean: 19.5 months), no complications associated with compression therapy were noted, and the authors recommended early initiation of compression therapy if the site of the lesion can be compressed.[248]

Totsuka et al. treated 3 girls with parotid gland hemangiomas (mean age: 4.3 months) by splinting using a resin plate and compression using a handmade cap. The mean duration of treatment was 13 months (8-16 months), and the patients were followed up until a mean age of 4.6 years (2-7 years), resulting in clinical and echographic disappearance of hemangioma in all 3. Since infantile hemangiomas often regress spontaneously, it is impossible to conclude that they regressed due to compression therapy, but they reported the therapy to be safe and effective.[249]

Thus, concerning factors related to “benefits” of compression therapy, there are reports that suggest the effectiveness of compression methods appropriate for sites (elastic bandages, Presnet, splinting with a resin plate). However, it must be noted that they are all old reports. Concerning factors related to “harms”, while compression is a relatively safe and simple method without reports of serious complications, the occurrence of dermatitis and growth disturbance at the site of compression or surrounding areas is considered possible. The recommendation level was set at 2D with consensus of the present guidelines preparation committee on condition that the treatment is performed carefully by a skilled physician in consideration of these points. The present guidelines do not exclude compression therapy, but it is necessary to consider oral propranolol, oral administration or local injection of steroid, and laser therapy first for infantile hemangiomas that need treatment.

CQ19: Is glucose transporter 1 (GLUT-1) immunostaining useful for the diagnosis of infantile hemangioma?

Recommendation:

Immunostaining for GLUT-1 is positive in the proliferating, involuting, and involuted phases, shows high sensitivity and specificity, and is useful for the diagnosis of infantile hemangiomas if the clinical diagnosis is difficult.

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| Strength of recommendation | 2 (weak) |
| Evidence | C (weak) |

Comments

To evaluate whether or not GLUT-1 immunostaining is useful for the diagnosis of infantile hemangiomas, the literature was searched first by the following key words.

Infantile OR juvenile AND hemangioma AND marker AND immunohistochemistry

The search of JCRM resulted in 26 hits, but none of them performed analysis of GLUT-1 or evaluated its usefulness by comparing infantile hemangioma with other hemangiomas/vascular malformations even if GLUT-1 was analyzed. The search of PubMed resulted in 182 hits. From these papers, those that deserved detailed analysis were selected according to the following criteria.

(1) Those in which GLUT-1 immunostaining was performed for infantile hemangioma or other hemangiomas/vascular malformations.

(2) Those that belonged to retrospective epidemiological studies rather than reports of one case.

Fifteen research papers selected by these criteria were analyzed in detail.

In 7 of these reports, infantile hemangiomas were stained using GLUT-1 simultaneously with other hemangiomas/vascular malformations, and differences in positive/negative results were evaluated.[250-256] Of all cases reported in the 7 papers, GLUT-1 was positive in 268 of the 273 cases of infantile hemangioma and negative in 244 of the 247 cases of lesions other than infantile hemangioma. There were also 4 papers in which GLUT-1 staining was performed for clinically typical infantile hemangiomas and hemangiomas that need to be differentiated from infantile hemangioma although they were not simultaneously stained in the same paper.[257-260] When the 4 papers were combined, GLUT-1 was positive in all 8 cases of infantile hemangioma and negative in all 49 cases of non-infantile hemangioma. When the above cases are totaled, GLUT-1 was positive in 276 of the 281 cases of infantile hemangioma and negative in 293 of the 296 cases of non-infantile hemangioma, and the sensitivity and specificity of GLUT-1 positivity for infantile hemangioma were 98.2 and 99.0%, respectively.

The usefulness of GLUT-1 staining has also been confirmed by re-evaluation of cases that initially examined by Hematoxylin-Eosin stain (HE stain) alone.[261-264] There have been 4 papers in which cases were re-evaluated using GLUT-1 staining, and 1 paper reported that the diagnosis was impossible by HE stain alone in 18% of the cases.[261]

CQ20: What gastrointestinal examinations are useful for children suspected to have blue rubber bleb nevus syndrome? When should the examinations be started?

Recommendation:

It is recommended to start screening by examinations including blood tests and fecal occult blood

test as early as possible. In children suspected to have gastrointestinal bleeding, the usefulness of endoscopic examination, red blood cell scintigraphy ($^{99m}$Tc-labeled red blood cells), and Single Photon Emission Computed Tomography-CT (SPECT-CT) has been reported for the identification of the source of bleeding. If no abnormality is detected by screening, and search for gastrointestinal lesions needs to be performed to diagnose this disease or evaluate the future risk of bleeding, there is no standard for its timing. Among the examinations that led to the detection of gastrointestinal lesions in past reports, CT and MRI can be performed with relatively mild invasion and from an early stage.

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| Strength of recommendation | 2 (weak) |
| Evidence | D (very weak) |

Comments

Gastrointestinal lesions of blue rubber bleb nevus syndrome (bean syndrome) are observed in the entire digestive tract, but they frequently appear, particularly, in the small intestine. Since it is an extremely rare disease, the literature is primarily case reports and reviews, and there have been no reports of clinical studies of many cases that are relevant for the CQ. Therefore, we investigated examinations that were useful for the detection of gastrointestinal lesions in reports, primarily, of child cases. Lesions in the small intestine are difficult to observe by conventional endoscopy, but techniques such as double-balloon endoscopy, capsule endoscopy, CT enterography, CT, and MRI as well as upper and lower gastrointestinal endoscopy have been reported to be useful.[265-275]

As a result of database searching, 11 papers in English were adopted through 1st and 2nd screening. All papers selected by these screening processes were case reports or case series, and the strength of evidence is “D (very weak)”.

There is no clear standard as to when the examinations should be initiated. However, neonates who developed gastrointestinal bleeding shortly after birth have been reported,[269] and the earliest possible examinations are desirable if this disease is suspected. Invasive examinations are difficult to perform in small children, but blood tests (presence or absence of anemia or consumption coagulopathy) and fecal occult blood tests can be performed. If gastrointestinal bleeding is suspected, procedures such as endoscopy, particularly, double-balloon endoscopy and capsule endoscopy, $^{99m}$Tc-labeled red blood cell scintigraphy, and $^{99m}$Tc-labeled red blood cell SPECT-CT have been reported to be useful for the determination of the source of bleeding.[265, 267, 270, 274]

If no abnormality has been detected by screening tests, and if search for gastrointestinal lesions needs to be performed non-emergently to diagnose this disease or evaluate the future risk of bleeding, there is no standard for the timing, which may vary among facilities. Among the above examinations, CT and MRI can be performed earlier and with relatively milder invasion, and are worth attempting if this disease is suspected. The necessity of the other examinations for the gastrointestinal lesions mentioned above should be considered when the patient reaches the age that tolerates the examinations.

CQ21: How are limb overgrowths to be managed in vascular malformations and syndromes?

Recommendation:

If leg-length inequality is insignificant, shoe lift is recommended. Significant inequality causes gait disturbance complicated with scoliosis, so surgical treatment aimed to arrest epiphyseal growth is performed in the growth period. Shortening of the femur or tibia may be performed as an additional treatment. Bone elongation of the intact side is considered effective for the correction of leg-length inequality.

Strength of recommendation 2 (weak)

Evidence D (very weak)

Comments

As a result of literature searches, 40 papers in English and 4 papers in Japanese were retrieved by primary screening. Of these papers, 17 in English and 4 in Japanese were extracted by secondary screening. As for the control of overgrowth of limbs, measures against leg-length inequality and soft tissue hypertrophy are separately discussed and regarded as effective, but these papers were all classified either as case reports or as general discussions. Therefore, the evidence level is rated as “very weak”, and the recommendation level as “weak”.

In vascular malformations, typical disorders with hypertrophy of the affected limbs are Klippel-Trenaunay syndrome and Parkes Weber syndrome and most of the papers refer to the management of limb overgrowth due to vascular malformations were written about these disorders. The literature regarding lesions at different sites is commented on below.

Lower limbs

In most reports, treatment for the overgrowth of the lower limbs were aimed to prevent physical disorders caused by leg-length inequality. Some reports particularly mentioned treatment for foot lesions.

## 1) Correction of leg-length inequality

If the leg-length inequality is ≤2 cm, the management of leg length difference and accompanying scoliosis is considered possible by the use of shoe lift.[276-280] If the leg-length inequality is ≥2 cm, significant gait disturbance, postural abnormalities, and compensatory change of the contralateral limb are likely to develop, and before consequent unphysiological gait leads to

irreversible impairment, surgical treatment to correct the leg-length inequality should be considered.[276-280] Long-leg radiography is useful for determining the best time for surgery,[281] and the measurement of the leg length by long-leg radiography or CT is reported to be effective.[277] Surgical treatment reported in the papers are as follows.

Treatment for overgrown limbs affected by vascular malformations

Jacob et al. performed epiphysiodesis in 41 patients with a leg-length inequality of ≥2 cm among 252 patients with Klippel-Trenaunay syndrome and reported improvement in more than 90% of the patients.[276] The effectiveness of this surgery is also affirmed by other review articles.[276-280] The effectiveness of shortening of the femur and tibia was reported in the review by Capraro et al.[277] The fixation period is considered to be shortened as a whole by simultaneously performing femoral or tibial shortening in addition to epiphysiodesis. Redondo et al. recommended endoscopic growth control of the epiphyseal plate in the distal end of the femur for patients with a leg-length inequality of ≥2 cm.[279] Capraro et al. did not recommend growth control with the epiphyseal stapling because of the unpredictability of the results and high frequency of complications.[277] The appropriate time for surgical intervention on affected limbs is reported to be around the age of 11 years.[279]

Elongation of the intact leg

Tanaka et al. performed bone elongation of the intact limbs using an external fixator in adult patients with mild structural scoliosis and reported that the procedure was effective for correcting the leg-length inequality and scoliosis.[282] Jacob et al. also recommended bone elongation of the intact limb using Ilizarov external fixation apparatus in their review.[276]

Popliteal vein ligation

Servelle hypothesized that elongation of the affected limbs was due to a high venous pressure and performed ligation of the popliteal vein of the intact limb in 48 children, and they reported significant improvement in leg-length inequality.[283] However, there are also negative views, saying its effectiveness is uncertain.[277]

2) Foot lesions

Redondo et al. recommended resection of the toes (ray resection) and debulking for wearing shoes and cosmetic improvement.[279] Gates et al. notably reported that compared with ray resection, wound healing of the stumps was poor after major resection.[284]

Upper limbs

Asymmetry due to hypertrophy of the upper limb less frequently causes impairment of ADL than that of the lower limb. In one article, resection in patients with functional impairment due to marked finger deformities is reported,[281] but articles reporting treatment for upper limb overgrowth is very few in number. While debulking has been reported to be advantageous from the cosmetic viewpoint,[278] it has also been reported to induce exacerbate of edema of the affected limb,[283] causing complications including cicatricial contracture, recurrence of the lesion, and refractory ulcer,[277] and sufficient caution is necessary.

CQ22: Is surgical resection effective for soft tissue/superficial LMs?

Recommendation:

Although surgical resection is an effective treatment, it should be applied after comprehensive evaluation of cosmetic aspects, prognosis, functional prognosis, resectability, and possibility of recurrence/complications.

Strength of recommendation 2 (weak)

Evidence D (very weak)

Comments

[Process of preparation of recommendation]

Surgical resection is one of the major treatment options performed for LMs. Although LMs can be cured by total resection, the objective of treatment is not necessarily total resection, because the disease is not malignant, and surgical resection is often carried out for cosmetic, functional, and symptomatic improvements. Cosmetic problems are considered to be particularly serious if the lesion is located in superficial areas such as the body surface and soft tissue. However, surgical resection has been known to cause complications including hemorrhage, infection, deformation, and nerve paralysis.

In evaluating whether resection is effective or not, the balance between its positive aspects and negative aspects, such as complications, is important. For soft tissue/superficial LMs, in which cosmetic improvement is important, problems including in what situations resection can be selected, whether there are criteria for the selection of resection, and, as there are differences in the incidence of complications, cure rate, and recurrence rate depending on the circumstances, whether its indications should be evaluated under different conditions are unclear. Therefore, the CQ, “Is surgical resection effective for soft tissue/superficial LMs effective?”, was formulated, and the current knowledge was summarized.

<Literature search and screening>

As a result of literature search, 105 papers in Japanese and 348 papers in English were

subjected to primary screening. Of these papers, 5 in Japanese and 42 in English were subjected to secondary screening concerning this CQ. They did not include papers with a high level of evidence, such as a systematic review and RCT, and all of them were case series or case reports. As a result, in the evaluation of this CQ, the results and discussion in each case series were integrated.

<Review of observational studies (case series)>

The effectiveness of resection of LMs was evaluated from the following 5 viewpoints: (1) Effectiveness regarding the life prognosis (mortality), (2) resection rate of the lesions (resectability), (3) functional outcome after resection (function), (4) recurrence rate (recurrence), and (5) complications.

Results of review

Generally, the rate of successful surgical resection is high, and ≥90% resection is reported to be possible in 60% or more of the patients.[285-287] This also applies to the head and neck region, which is the frequent site of the lesion.[285] However, the percentage of resectable lesions decreases from the cystic to mixed and to cavernous type.[285] Since many LMs are distributed diffusely in the skin and subcutaneous adipose tissue and around structures including muscles, blood vessels, and nerves, resection of the lesion involves resection of normal tissues in varying degrees. In lesions that show complicated distribution in the head and neck region, complications after surgical resection are observed relatively frequently. Serious complications including nerve paralysis, hematoma, local necrosis, sepsis, deformation, salivary fistula, hoarseness, airway obstruction, and malocclusion have been reported,[285, 286, 288-296] and facial nerve paralysis is likely to result from resection, particularly, of LMs infiltrating the parotid region.[288] By the site, the incidence of complications increases as the area of involvement widens from unilateral to bilateral, from below to above the lingual bone, both

sides, and both above and below the lingual bone.[292, 295] Postoperative death is possible in patients with a severe neck lesion, but the extent of the effect of surgical resection is unclear.[286, 287, 297] Postoperative recurrence is closely related to the resectability of the lesion depending on its distribution, and lesions that are difficult to resect due to a wide area of involvement and a strong tendency of infiltration have been reported to be associated with recurrence.[295]

Limitations

Indications for surgical resection vary among papers, and differences in the patient background must be considered in the evaluation of the effectiveness of resection. While there were many reports that surgical resection was performed in combination with sclerotherapy, and resection is considered to have been selected when more favorable results were expected from resection rather than sclerotherapy, criteria for their selection are unclear. Therefore, there is certainly the large bias of individual variation in the circumstances, and it was clearly impossible to conclude that resection is uniformly effective.

<Summary>

While the effectiveness of surgical resection for soft tissue/superficial LMs was evaluated, there was no literature with a high level of evidence. One of the major reasons is the diversity of the lesion type (cystic or cavernous), area of involvement, history of other treatments, etc. Because of this diversity, the condition of patients is considered to show an extremely wide variation, and their generalization is impossible. However, if conditions, such as the type of the lesion (cystic or cavernous), site of origin, and relationship with other treatments are restricted, tendencies were observed in functional prognosis, recurrence rate, and contents and incidence of complications.

While the resection rate of lesions by surgical treatment was suggested to be generally high,

selection criteria for resection were unclear. Therefore, it is speculated that resection tended to be selected for patients clinically judged to be treated more effectively by surgery. However, since there were some serious complications of surgical resection that persist as sequelae, their possibility should be evaluated carefully in applying surgical resection. The risk of resection has been suggested to vary with conditions of the lesion. The functional outcome is poor, and the recurrence rate and incidence of complications after resection are high, in those that occupy a wide area and those that are accompanied by symptoms such as airway obstruction.

From these observations, we propose at present, “While surgical resection is often effective, it must be selected in consideration of cosmetic aspects, life prognosis, functional prognosis, resectability, and possibility of recurrence and complications.”, despite limited scientific grounds. If complete resection of the lesion is possible, surgical resection may be performed as the first line treatment, but the possibility of other treatments including sclerotherapy, in particular, should be evaluated according to the diverse conditions of individual patients, and surgical resection should be selected when other treatments are ineffective or when surgical resection is considered clearly superior.

CQ23: What is the optimal timing of surgery for soft tissue/superficial LMs?

Recommendation:

It is impossible to recommend optimal timing of surgery, and judgments according to the condition of each case are necessary.

| | |
|---|---|
| Strength of recommendation | 2 (weak) |
| Evidence | D (very weak) |

Comments

[Process of preparation of recommendation]

Soft tissue/superficial LMs are not malignant lesions. Emergent treatment may be necessitated by life-threatening symptoms, such as airway obstruction, but the initiation of treatment immediately after the diagnosis is generally considered unnecessary. The natural course of the disease differs considerably among individuals, particularly, in infancy, and the lesions may show tendency of spontaneous regression but may also cause various functional problems due to rapid enlargement. Moreover, there are cosmetic problems characteristic of this disease in addition to functional problems, and early therapeutic effects are desirable to make social life comfortable. For these reasons, the selection of optimal timing of treatment, surgery in particular, is a major issue.

For the selection of the timing of surgical resection, conditions to obtain the best results as well as indications for resection must be evaluated, and sufficient consideration of the balance between merits and demerits depending on the timing of resection is necessary. Therefore, in this CQ, we attempted to summarize the presently available knowledge about “What is the optimal timing of surgery for soft tissue/superficial lesions?”.

<Literature search and screening>

As a result of literature search, 67 papers in Japanese and 231 papers in English were subjected to primary screening. Of these papers 5 in Japanese and 42 in English were subjected to secondary screening for this CQ. They included none with a high level of evidence, such as a systematic review and RCT, and all papers were case series or case reports. Therefore, the results and discussion in each case series were integrated in the evaluation of this CQ.

<Review of observational studies (case series)>

Defining “the optimal timing of surgery” mentioned in the CQ as “the timing of surgery at which good results can be obtained”, we aimed to evaluate the timing of surgery at which resection is effective, problems, such as complications are few, and, ie, “the best results” can be obtained as a whole. Conditions must be evaluated on the basis of the timing in addition to the effectiveness of surgery, but objective judgments were considered difficult in this evaluation. However, as it was considered possible to obtain information about the age and time of surgery from the literature reviewed in the previous CQs concerning the effectiveness, papers that evaluated the age at surgery were searched.

Results of review

Despite a careful review of the literature by secondary screening, there was no paper that analyzed cases from the viewpoint of optimal timing of surgery. There was information concerning the age at surgery, but its appropriateness was not evaluated. Papers that mentioned the timing of surgery are shown below.

Concerning the timing (age) of surgery, unless the size of the lesion is small or there are symptoms that require urgent treatment, such as respiratory disturbance, it is recommended to wait to apply surgery until the age of 3 years by expecting spontaneous regression or for the ease of identification of surrounding structures during surgery, ease of control of bleeding, and less trouble of postoperative management.[293] There was also a paper that suggested the necessity of the determination of the time of surgery in consideration of problems that change with age including the priority of securing the airway and appropriate nutritional management in neonates with head and neck and giant lesions, control of hemorrhage and infection and measures to prevent dysarthria and dental problems in infants, and skeletal and cosmetic problems in school-age children, although it did not mention the optimal timing of surgery.[294]

However, there was no paper that positively recommended resection without considering the time after the diagnosis or grounds for such a recommendation.

<Summary>

As a result of literature search for evaluating the CQ, “What is the optimal timing of surgery for soft tissue/superficial LMs”, there were papers that mentioned the timing of surgery, but none of them objectively evaluated its appropriateness. Therefore, no suggestion about the appropriate timing of surgery could be obtained from the literature available at present, but there were a few papers suggesting that the decision to perform surgery should be made carefully.

Similar to the previous CQ, soft tissue/superficial LMs of which the background vary in individual cases, and it is difficult to uniformly evaluate the effectiveness of resection. In clinical practice, in addition to medical reasons, social reasons including school attendance are considered to largely influence the decision of the time of resection. The results of RCTs are necessary to obtain objective data, but it is practically very difficult to arrange an RCT fulfilling the above conditions.

While this CQ is a very important issue for patients and families as well as clinicians, there has not been objective evaluation of the optimal timing of surgery in the past. Presently, rough and ready decisions to perform surgery should be avoided, so this guideline proposes, “The optimal timing of surgery cannot be decided in general, and judgments according to the condition of each case are necessary.”

CQ24: Is sclerotherapy effective for facial microcystic LMs?

Recommendation:

A wide range of drugs are used for sclerotherapy. Although comparison among drugs has not been made, and consensus regarding the methods or frequency of their administration has not been

formed, improvements are observed after sclerotherapy in various symptomatic, functional, and cosmetic (esthetic) aspects. However, complications including functional impairment have also been reported.

| | |
|---|---|
| Strength of recommendation | 2 (weak) |
| Evidence | D (very weak) |

Comments

[Process of preparation of recommendation]

[Literature search and screening]

Concerning this CQ, 35 papers in Japanese and 92 papers in English (60 from PubMed, 32 from Cochrane) were retrieved. After their primary screening, 6 in Japanese and 18 in English were subjected to secondary screening concerning this CQ. Although they included 3 RCTs, many of the other papers were case series or case reports. Therefore, in the evaluation of the draft recommendation concerning this CQ, the results and discussion in each RCT and case series were integrated. While the evidence is deficient, the papers judged to be useful for the preparation of the draft recommendation are presented as review data.

[Review of case series]

As a result of literature screening, it was found that the effectiveness of sclerotherapy for facial microcystic LMs has been evaluated from the following viewpoints.

(1) Treatment responses

A. Size

B. Symptoms

C. Functions

D. Cosmetics

(2) Complications

The contents of the accounts concerning the effectiveness of sclerotherapy are summarized according to these viewpoints.

However, there were few reports that exclusively analyzed facial (and microcystic) LMs, and lesions of the neck and other regions as well as the face were evaluated or different types of LMs, such as cystic and mixed types, were reported together. In addition, the definition of the cavernous type and standard procedure of sclerotherapy (method and number of administrations) varied among reports, and these differences in the background should be considered in the evaluation of the effectiveness of sclerotherapy.

The sclerosing agents used for the literature search ranged widely from OK-432, bleomycin, ethanol, doxycycline, and sodium tetradecyl sulfate (STS). However, as none of the papers reviewed for the preparation of this guideline evaluated differences in the effectiveness for facial microcystic lesions among drugs or the method or number of administrations of each drug, these evaluation items were excluded in discussing this CQ.

(1) Responses

A. Size

Many of the papers that referred to the regression rate of the lesion classified the responses into (1) excellent or complete (regression rate ≥90%), (2) good or substantial (regression rate ≥50% and <90%), (3) fair or intermediate (regression rate ≥20% and <50%), and (4) poor or none

(regression rate <20%).

Although there was no paper that collected cases of facial lesions alone, Yang et al. reported that the regression rate after sclerotherapy was ≥90% in 19 (63%) of the 30 patients with head and neck lesions and ≥50% in 10 (33%).[298] In addition, the regression rate was reported to be ≥50% in 18 (85.7%) of the 21 patients with head and neck lesions by Alomari et al.[299] and in 30 of the 31 patients to be ≥50%, who included those with mixed type lesions, by Chaudry et al.[300]

Smith et al. reported that none showed a response (complete or substantial) in 17 patients who underwent sclerotherapy, some of whom had mediastinal lesions.[301] Giguere et al. also reported that all 5 patients with head and neck lesions showed no response (poor) to the therapy.[302] While these studies were RCTs evaluating the time of sclerotherapy, the results suggest that sclerotherapy is not effective for microcystic lesions regardless of the time of treatment.

There was no paper that compared sclerotherapy and resection for facial microcystic LMs.

B. Symptoms

There is no literature that evaluated this item based on objective data, and few reports referred to symptoms themselves. The information was limited to the report by Chaudry et al.[300] that symptoms disappeared after sclerotherapy using bleomycin in 75% of the patients who complained of pain and a few case reports that symptoms, such as hemorrhage and respiratory impairment, were relieved after sclerotherapy.[303, 304]

C. Functions

Ravindranathan et al. performed sclerotherapy in 3 patients with diffuse microcystic lesions extending from the face to the tongue and pharynx and reported that respiratory impairment and swallowing disorder due to airway stenosis observed before treatment were mitigated.[305]

Poonyathalang et al. administered sodium tetradecyl sulfate (STS) to a patient with orbital lesions primarily complaining of visual defect and reduced visual acuity due to retrobulbar hemorrhage and reported alleviation of the symptoms,[306] but appropriate literature was scarce similar to that concerning symptoms.

D. Cosmetic aspects

Cosmetic improvements are difficult to evaluate objectively. Poonyathalang et al. administered STS to 3 patients with orbital lesions with exophthalmos as the primary symptom and reported improvement by measuring the degree of protrusion before and after the treatment.[306] There have also been reports of objective assessment based on the degree of satisfaction in the patients' families. According to Chaudry et al.,[300] all patients with head and neck lesions (9 with microcystic lesions, 22 with mixed lesions) and their families reported improvements in the size and appearance of the lesions. In addition, Alomari et al. treated 32 patients with mostly microcystic but including some cystic LMs of the head and neck region by sclerotherapy and reported improvements compared with the condition before treatment by the families of 26 patients (81.3%).[299]

(2) Complications

As complications in the facial region, there are a large number of reports of transient complications associated with sclerotherapy, such as fever, local swelling and pain, intracystic hemorrhage, and infection, although the lesions were poorly characterized in some reports.[298, 300, 306-311] In addition, complications considered to have been caused by the effect of treatment, such as ulcer of the oral mucosa and tongue, facial nerve paralysis, leakage of saliva, and respiratory insufficiency due to airway obstruction, have been occasionally reported.[302, 305, 306] There have also been reports of an elevation of the intraorbital pressure, exophthalmos, intraorbital hemorrhage,

corneal damage, and external ocular muscle paralysis due to enlargement of the mass after sclerotherapy for ocular LMs.[306, 312, 313] There was also no literature showing the incidence of complications in facial microcystic LMs.

As complications caused by sclerosing agents, skin ulcer and necrosis and nerve damage due to ethanol leakage, hypotension during anhydrous ethanol injection, and epidermal detachment due to doxycycline have been reported.[299, 314] However, there was no report of serious complications due to OK-432. Pulmonary fibrosis is widely known to be a complication of bleomycin, but, according to Chaudry et al.[300] and Yang et al.,[298] impairment of respiratory function does not occur at a dose usually employed for sclerotherapy.

[Summary]

In evaluating the CQ, “Is sclerotherapy effective for facial microcystic LMs?”, analysis was performed from the viewpoints of responses to the treatment in terms of symptoms, functions, and cosmetic (esthetic) aspects and complications, but few papers with a high level of evidence were found. While the degree of regression of the lesions by sclerotherapy varied widely, the size-reducing effect of the therapy was consistently small unlike that in cystic lesions. Some papers referred to symptoms, functional outcome, and cosmetic improvement, but they were insufficient for general discussion of sclerotherapy for facial microcystic LMs. As complications characteristic of sclerotherapy, serious impairment may be caused by leakage of the sclerosing agent (ethanol, in particular), and this point needs attention. Based on the above observations, it is difficult at present to evaluate indications for sclerotherapy against microcystic LMs by formulating criteria. Therefore, for the future, it is considered necessary to evaluate the usefulness of sclerotherapy addressed by this CQ by designs such as RCT.

CQ25: Is sclerotherapy effective for intra-abdominal LMs?

Recommendation:

Although there are many reports that sclerotherapy is useful, there is the risk of complications, and careful judgments about matters including the resectability of the lesion and selection of the sclerosing agent are necessary.

| | |
|---|---|
| Strength of recommendation | 2 (weak) |
| Evidence | D (very weak) |

Comments

[Process of preparation of recommendation]

LMs are the most frequent lymphatic vessel disorders of the abdomen. Intra-abdominal lesions are estimated to account for 10-20% of all LMs, and the selection of treatment is difficult depending on the site of the lesion. While surgical resection is expected to be effective, less invasive treatments are considered desirable in view of stress to the patient and the possibility of severe complications such as lymphatic fluid leakage and bowel obstruction. Sclerotherapy, which is a major treatment for LMs, is considered to be less invasive than surgery. Although positive therapeutic effects are expected, sclerotherapy is known to induce marked inflammation. And whether it can be performed safely without negative effects including complications and its long-term effects are major clinical concerns. In addition, what therapeutic effects are expected or what complications should be anticipated after sclerotherapy for the intra-abdominal lesion is also unclear. Therefore, the CQ, “Is sclerotherapy effective for intra-abdominal LMs?”, was formulated, and knowledge available at present was compiled.

<Literature search and screening>

As a result of literature search, 19 papers in Japanese and 38 papers in English (32 from PubMed, 6 from Cochrane) were subjected to primary screening. Of these papers, 2 in Japanese and 9 in English were subjected to secondary screening concerning this CQ. They included no papers with a high level of evidence, such as systematic reviews and RCTs, and all were case series or case reports. Consequently, the results and discussion in each case series were integrated in the evaluation of this CQ.

<Review of observational studies (case series)>

The literature concerning the effectiveness of sclerotherapy for intra-abdominal LMs was reviewed from the viewpoints of (1) therapeutic effects (decrease in lesion size, symptoms) and (2) complications.

The drugs used for sclerotherapy ranged widely from OK-432 to bleomycin, ethanol, doxycycline, STS (sodium tetradecyl sulfate), acetic acid, steroid/tetracycline, and 50% glucose solution. According to our review, there was no paper that evaluated the differences in effectiveness of sclerotherapy in the abdomen according to the drug type or administration method or number of administrations of each drug.

Results of review

(1) Therapeutic effects

A. Regression rate of the lesion

Regression of lesions of intra-abdominal LMs by sclerotherapy was mentioned in 5 papers.[287, 315-318] According to the report by Chaudry et al.,[315] the reduction rate was ≥90% in 7 and ≥20% in 1 of the 10 patients with LMs of the mesentery and retroperitoneum treated with

doxycycline, and evaluation using imaging examination was not performed in 2 cases. The patient who showed a low regression rate had a mixed type of cystic and cavernous lymphangiomas, and the other patients had cystic lesions. Oliveira et al. reported that the lesion regressed by 70% in 1 of the 2 patients with cystic lymphangiomas treated with OK-432.[316] Won et al. reported 1 patient who showed complete disappearance of cystic retroperitoneal lesions after sclerotherapy using acetic acid.[317] Shiels et al. reported that cystic lesions responded to sclerotherapy using STS and ethanol in 2 patients, but there was no mention about the reduction rate.[318] However, according to Alqahtani et al., no effect was observed in 10 patients who underwent sclerotherapy using steroid/tetracycline or 50% glucose solution.[287]

B. Symptoms

There were 3 papers that referred to symptoms of patients treated by sclerotherapy for intra-abdominal LMs.[315, 316]

According to Chaudry et al.,[315] of the 10 patients who underwent sclerotherapy, 3 had chronic abdominal pain, 3 had acute abdominal pain, 1 had fever/chill, 1 had anemia, and 2 had palpable masses, but the symptoms were alleviated by treatment in all patients, and no recurrence was noted.

Oliveira et al. reported that sclerotherapy was performed in a patient with a palpable mass and in one with a palpable mass, abdominal compartment syndrome, and a poor general condition. While the condition was alleviated in the patient who only showed a palpable mass after 2 courses of OK-432 sclerotherapy, but the treatment was changed to surgery in the patient who had abdominal compartment syndrome because of enlargement of the mass due to intracystic hemorrhage.[316]

(2) Complications

Three papers specifically mentioned complications of sclerotherapy for intra-abdominal LMs. There was no report of deaths due to treatment-related complications. Oliveira et al. treated 3 patients by sclerotherapy using OK-432 and reported that one of them developed subbowel obstruction after the treatment and another required emergency surgery due to exacerbation of abdominal compartment syndrome induced by intracystic hemorrhage.[316] Chaudry et al. reported that doxycycline used for sclerotherapy leaked into the retroperitoneal space in 1 of the 10 patients but that the lesion regressed without any particular problem.[315] Won et al. performed sclerotherapy using acetic acid in 1 patient with retroperitoneal cystic lymphangioma. Although pain and hematuria were observed, they concluded that the relationship of hematuria with the therapy was unclear, because it was observed during menstruation.[317]

Limitations

Sclerotherapy was often performed before, after, or during surgical resection, and papers that reported the results of sclerotherapy alone were few. There was no paper that directly compared observation without treatment, sclerotherapy, and surgical resection. Few papers analyzed intra-abdominal lesions alone, and many papers included lesions in other areas or evaluated lesions in different intra-abdominal regions including the mesentery, retroperitoneum, and viscera collectively.

Moreover, differences in properties of LMs, such as cystic, cavernous, and mixed types, their definitions, criteria for the selection of sclerotherapy (combination with surgery, types of sclerosing agents and methods of their use, number of administrations, etc.) varied among papers, and few papers evaluated these matters separately.

Such differences in the patient background and contents of treatment must be considered in evaluating the effectiveness of sclerotherapy. In evaluating this CQ, particularly, differences in

morphology of LMs and sclerosing agents were excluded.

<Summary>

The CQ, “Is sclerotherapy effective for intra-abdominal LMs?” was evaluated from the viewpoints of therapeutic effect, symptoms/functions, and complications, but no paper with a high level of evidence was found. While sufficient regression of the lesion and alleviation of symptoms were achieved by sclerotherapy in some patients, the response rate varied among reports, and information was insufficient for general discussion of sclerotherapy. Concerning treatment-related complications, there have been reports of bowel obstruction associated with sclerotherapy, and attention to this condition as well as intracystic hemorrhage is considered necessary. However, there was no report of chylorrhea, which was reportedly caused by surgery.

Based on the above observations, it is presently difficult to determine indications for sclerotherapy in intra-abdominal LMs by setting up criteria, but as there was no literature that strongly denied intra-abdominal LMs as indications of sclerotherapy, this guideline proposes, “Although there are many reports that sclerotherapy is useful, there is the risk of complications, and careful judgments about matters including the resectability of the lesion and selection of the sclerosing agent are necessary.” For the future evaluation of this CQ, validation by a design with a high level of evidence, such as RCT, is considered necessary.

CQ26: Are patients with scarcely symptomatic intra-abdominal LMs recommended to be treated?

Recommendation:

Since there is risk of treatment-related complications, it is proposed to consider therapeutic intervention when the lesion tends to enlarge or has become symptomatic.

Strength of recommendation 2 (weak) Evidence D (very weak)

Comments

[Process of preparation of recommendation]

Intra-abdominal LMs occasionally present with severe symptoms such as abdominal pain, giant mass, and bowel obstruction but may also be asymptomatic and detected incidentally. Lesions may gradually enlarge and cause serious symptoms due to infection and intraluminal hemorrhage.

Under such circumstances, whether or not patients with nearly asymptomatic intra-abdominal LMs should be aggressively treated, when they should be optimally intervened during their long follow-up period, etc., are major problems that pose clinical dilemma. Therefore, the CQ, "Are patients with scarcely symptomatic intra-abdominal LMs recommended to be treated?", was formulated, and knowledge available at present was summarized.

<Literature search and screening>

As a result of literature search, 206 papers in Japanese and 237 papers in English (230 from PubMed, 7 from Cochrane) were subjected to primary screening. Of these papers, 6 in Japanese and 9 in English were subjected to secondary screening concerning CQ 26. They included no study with a high level of evidence, such as a systematic review or RCT, and many of them were case series or case reports. Since 7 papers among them described asymptomatic LMs, their results and discussions were integrated to answer the CQ.

<Review of observational studies (case series)>

Seven papers among reviewed literature described about asymptomatic LMs.[315, 316, 319-323] Fifteen cases reported in these papers were considered to have actually presented few symptom

(including asymptomatic patients who were incidentally detected by imaging studies to have intra-abdominal masses at the sites as greater omentum, mesentery and retroperitoneum).

The literature was screened, and papers addressing issues concerning therapeutic intervention for scarcely symptomatic intra-abdominal LMs including "What symptoms they may present with if they are left untreated?", "By what studies and how often should they be examined?", and "What other treatments are available and how serious are complications or risk of each treatment?" were reviewed.

Results of review

From the literature reviewed, symptoms of intra-abdominal LMs (abdominal pain, bowel obstruction, torsion, infection, hemorrhage, vomiting/sucking difficulty, frequent urination and abdominal mass[319-325]) are considered to be dependent on factors such as site, size and age. It is desirable to determine risk factors by stratification of these factors in the future.[319, 321, 324]

Reported complications in treated cases include recurrence that required re-treatment,[320] bowel obstruction,[316, 322, 323] chylous ascites,[323, 325] embolism,[316] hemorrhage[316] and wound infection. Embolism of the inferior vena cava after surgery[316] and abdominal compartment syndrome after adhesion therapy[316] were reported as severe complications. It deserves special attention that, if surgical resection is selected for mesenteric LMs, the intestine may have to be resected with the lesion.[325]

While there have been reports that intra-abdominal LMs with few clinical symptoms regressed during follow-up,[319, 321] they may become symptomatic later (as observed in many case reports). For that reason, the opinion that intervention should not been chosen during the follow-up until the lesion enlarges or new symptoms appear was frequently described.

Limitations

It should be noted that many asymptomatic cases can possibly be left unreported and some asymptomatic lesions that are detected were treated. There is no study with a high level of evidence indicating explicit criteria concerning the age, site or situation about whether or not intervention should be made for asymptomatic intra-abdominal LMs.

<Summary>

The necessity of treatment of a patient with intra-abdominal LMs with few symptoms should be determined after evaluating the balance between the risk of treatment and non-treatment considering its site and size as well as patient age. However, since research on indications for treatments has been insufficient so far and serious complications after treatment have been reported, deliberate evaluation for each patient is mandatory. When observation is selected, periodic imaging studies are recommended to optimize therapeutic intervention by detecting enlargement of the lesion. And also if any symptom has developed during follow-up, intervention should be considered. For these reasons, the recommendation, “Since there is risk of treatment-related complications, it is proposed to consider therapeutic intervention when the lesion tends to enlarge or has become symptomatic.” was adopted.

CQ27: What are treatments effective for refractory chylous ascites?

Recommendation:

Conservative treatments, such as fasting, high-calorie infusion, and medium chain triglyceride (MCT), should be performed first, but, if they are ineffective, drug treatment, sclerotherapy, and surgery may also be considered.

Strength of recommendation 2 (weak)

Evidence D (very weak)

Comments

[Process of preparation of recommendation]

Refractory chylous ascites causes loss of large amounts of protein and lymphocytes, decreases in the blood lipid levels, and abdominal pain, unpleasantness, and dyspnea due to abdominal distention and markedly reduces the patient quality of life (QOL). The cause of ascites often remains unknown. Treatment of chylous ascites may require drainage to avoid abdominal distention. It is a very important point for clinicians to make proper judgments by understanding treatments and their effects and demerits. Therefore, it is considered beneficial to collect information about chylous ascites over a long period and compile guidelines. For this purpose, the presently available knowledge was collected by formulating the CQ, “What are treatments effective for refractory chylous ascites?”

<Literature search and screening>

As a result of search, 161 papers in Japanese and 728 papers in English (564 from PubMed, 164 from Cochrane) were subjected to primary screening. Of these papers, 15 in Japanese and 12 in English were subjected to secondary screening for CQ 27. They included none with a high level of evidence, such as systematic reviews and RCTs, and consisted of 1 multicenter and 2 single-center case series and case reports. Consequently, we used the results and discussion of 27 papers judged for the preparation of the draft recommendation were integrated although evidence was insufficient for the evaluation of this CQ.

<Review of observational studies (case series)>

As for causes of chylous ascites, congenital chylous ascites,[326-341] idiopathic chylous ascites,[327] chylous ascites after laparotomy,[342-345] protein-losing enteropathy,[344] LMs,[346, 347] lymphangiectasis,[348, 349] lymphangiomatosis,[350, 351] and lymphatic dysplasia[352] were reported. None of the papers evaluated treatments according to the cause.

When treatments are categorized, conservative treatments (fasting, high-calorie infusion, medium chain triglyceride (MCT)), drug treatments, sclerotherapy, and surgical treatment were performed.

Results of review

The results of review are presented below according to the treatment.

(1) Conservative treatments

Whether or not the amount of ascites changes by fasting should be checked first.

High-calorie infusion is often used with fasting, and since there was no report that ascites increased under the effect of high-calorie infusion according to our review, it is recommended for nutritional support during fasting. In the multicenter case series reported by Bellini et al., high-calorie infusion/total parenteral nutrition was performed in 15 patients without adverse effects.[326]

MCT was used before, after, and during treatment.[326, 327, 329-334, 336, 338-340, 342, 344, 345, 347-351] In the multicenter case series by Bellini et al., MCT was reportedly performed in 14 patients without adverse effects.[326]

(2) Drug treatments

In drug therapy for chylous ascites, primarily octreotide (a long-acting somatostatin

analogue) was used, and no report that discussed the effectiveness of other drug therapies was found by the present literature search.

In the multicenter case series by Bellini et al., octreotide was administered to 6 of the 16 patients with chylous ascites for 8-38 days, and a decrease in chylous ascites was reported in all of them.[326] In the single-center case series by Huang et al., 2 of the 4 patients with chylous ascites treated by high-calorie infusion and octreotide administration were reported to have shown a decrease in ascites within 10 days.[343] However, there has been a report that no effect was observed despite the administration of octreotide for 3 weeks.[329] Concerning the dose of octreotide, it was administered at 1 μg/kg/h,[326] at 3 μg/kg/h,[331] began to be administered at 0.5 μg/kg/h and increased to 10 μg/kg/h by 1 μg/kg/h,[328] administered by continuous intravenous infusion at 0.5-2.0 μg/kg/h,[332] and began to be administered by subcutaneous injection at 2.5 μg/kg 2 times/day and increased every 2 days to 8 μg/kg 2 times/day.[329] Regarding the time of the beginning of administration, the administration was started as no improvement was observed in chylous ascites after conservative treatments for 2 weeks,[329, 333] and as chylous ascites was alleviated by conservative treatments but was exacerbated again.[332] No adverse effects of octreotide administration were noted in the present review of the literature. Thus, no control study that evaluated the effect of octreotide on chylous ascites was found by the present literature search, and the level of evidence concerning the efficacy is low, but as there are case series and many case reports that chylous ascites was reduced by octreotide administration, it appears reasonable to consider drug treatment using octreotide for chylous ascites that does not respond to conservative treatments.

(3) Sclerotherapy

Sclerotherapy was performed in 6 patients in 5 case reports.[338, 346, 348, 350, 351] The sclerosing agent was OK-432 in 5 of the 6 patients and was Beta-Isadona-solution in 1.[348] OK-432 was locally

injected into the lesion in 4,[346, 350, 351] administered intraperitoneally in 1,[351] and administered via the drain in 2.[346, 351] Concerning sclerotherapy, the number of reported cases that could be reviewed was limited, and further accumulation of cases is considered necessary to establish its usefulness.

(4) Abdominal drainage, abdominal puncture, and surgical treatment

Abdominal drainage and abdominal puncture are performed when organ compression symptoms (compartment syndrome and respiratory insufficiency) due to abdominal distention are present or possible or when the drain is inserted postoperatively. However, drainage itself cannot improve chylous ascites, and treatments, such as infusion, blood preparations, and blood transfusion, are necessary to supplement the ascites lost due to drainage.[326, 329-332, 336-339, 342, 344-346, 348, 350, 351]

Surgical treatment is reported to be frequently performed after conservative or drug treatments. According to the single-center case series by Zeidan et al., surgical treatment was performed in patients who responded poorly to conservative treatments continued over a mean of 25.3 days.[342] In other reports, surgical treatment was performed after conservative treatments continued for 1-3 months[327, 328] and in patients with congenital chylous ascites 1-4 months after birth.[329, 333, 349] Since it is often impossible to identify the leakage site of chylous ascites,[329] attempts to identify the leakage site by orally administering a lipophilic dye (Sudan black, Sudan III) before operation. [327, 328, 335, 342] When the leakage site can be identified, ligation, suturing, clipping, and cauterization have been performed.[327, 333, 335, 342, 349] In addition to reports of the usefulness of techniques to stop leakage, such as applying or sprinkling fibrin glue at the leakage site of chylous ascites or over the surrounding retroperitoneum[328, 330, 342, 349] and applying a patch of oxidized cellulose/resorbable local hemostatic agent,[330, 342] there have also been reports of peritoneovenous shunting[348, 352] and peritoneoamniotic shunting for fetal cases.[337]

There was no large clinical study in the past literature. Therefore, although the level of

evidence is low, we consider that surgical treatment is recommendable for chylous ascites that does not respond to conservative or drug treatments, because it has been performed in case series and case reports for chylous ascites that did not respond to conservative or drug treatments continued over about 1 month. Although techniques to enhance the response rate of surgical treatment, such as identifying the leakage site by using a lipophilic dye and applying fibrin glue or a patch of oxidized cellulose/resorbable local hemostatic agent, have been attempted, there are only case series and case reports, and none of the papers retrieved by the present literature search evaluated their usefulness.

Limitations

There was no literature that defined refractory chylous ascites based on the duration of illness or treatment responses. Therefore, we extracted and summarized factors that were considered to contribute to clinical refractoriness, such as the duration of illness and treatment responses, in each paper related to the treatment for chylous ascites. Also, as the cause of chylous ascites varies widely, the therapeutic effect is expected to differ depending on the cause, but no paper that could be reviewed evaluated treatments according to the cause. Therefore, in the present evaluation, the statements are limited to treatments and their effects regardless of the cause.

<Summary>

It was difficult to comprehensively discuss treatments, because its cause varied widely, and treatments for various causes were performed. Therefore, treatments were classified into conservative treatments (fasting, high-calorie infusion, MCT), drug treatments (octreotide), sclerotherapy, abdominal drainage, abdominal puncture, and surgical treatment, and the effects of each treatment were evaluated.

Treatments effective for refractory chylous ascites can be summarized as follows with the

understanding that they may depend on the cause and that the level of evidence of the available reports concerning treatments and their effects is low. Conservative treatments, such as fasting, high-calorie infusion, and MCT, should be performed first because of the rareness of adverse effects. In patients who respond insufficiently to conservative treatments, drug treatments using octreotide can be considered as there have been case series and many case reports. Concerning sclerotherapy, the number of reported cases is small, and further large clinical studies will be needed to confirm its usefulness. Abdominal paracentesis and surgical treatments may be considered for chylous ascites that does not response to conservative or drug treatments continued for about 1 month.

Thus, the draft recommendation is “Conservative treatments, such as fasting, high-calorie infusion, and MCT, should be performed first, and, if they are ineffective, drug treatments, sclerotherapy, and surgical treatments may be considered.” However, evaluation of this CQ by a design with a higher level of evidence, such as RCT, is considered necessary for the future.

CQ28: What kinds of complications are associated with treatments for intra-abdominal LMs?

Recommendation:

Complications associated with sclerotherapy for intra-abdominal LMs include bowel obstruction, hemorrhage, pain, hematuria and chylous ascites. Operative treatment of the disease can be associated with serious complications such as occlusion of the inferior vena cava and massive resection of the intestine as well as more common, wound infection, bowel obstruction, hemorrhage and chylous ascites.

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|---|---|
| Strength of recommendation | No recommendation |
| Evidence | D (very weak) |

Comments

[Process of preparation of recommendation]

Patients with intra-abdominal LMs are treated with various modalities from non-operative therapy to surgical procedures. Treatment modality is selected depending on the patient's state. Therefore, it is necessary for the clinician, patient, and family to share information concerning complications that may be associated with treatments for smoothly implementing them. However, there are no resources that give a clear answer to this problem, and both clinicians and patients tend to be baffled. Therefore, the CQ "What kinds of complications are associated with treatments for intra-abdominal LMs?" was formulated, and information available at present was accumulated and integrated for the answer.

<Literature search and screening>

As a result of literature search, 203 papers in Japanese and 602 papers in English (593 from PubMed, 9 from Cochrane) were subjected to primary screening. Of these papers, 23 in Japanese and 27 in English were subjected to secondary screening concerning this CQ. They included no papers with a high level of evidence, such as systematic reviews or RCTs, and all of them were case series or case reports. To answer CQ 28, the results and discussion in each case series were integrated.

<Review of observational studies (case series)>

Complications in the CQ were evaluated by defining them as those encountered when patients with intra-abdominal LMs were treated, and reports on sclerotherapy and surgery were reviewed.

Results of review

(1) Complications associated with sclerotherapy

Sclerotherapy using OK-432 was reported to be associated with bowel obstruction and hemorrhage for mesenteric LMs,[316] and chylous ascites for retroperitoneal LM.[325] Sclerotherapy using acetic acid was reported to be associated with pain and hematuria in patients with retroperitoneal LMs.[317]

(2) Complications associated with surgical procedures

Complete resection of both mesenteric and retroperitoneal LMs by laparotomy was reported to be associated with wound infection[323, 353] and bowel obstruction[322, 353, 354] as common complications. There were reports of serious complications such as occlusion of the inferior vena cava[316] and massive resection of the intestine necessitated due to diffuse infiltration of the LM tissue to the intestinal wall.[355]

In a report about complications associated with complete laparoscopic resection of intra-abdominal LMs by Tran et al., resection was attempted in 47 patients, and conversion to laparotomy was necessary in 3 (6.4%) due to tight adhesion in 2 and intraoperative hemorrhage in one.[356]

Partial resection by laparotomy was reported to be associated with persistent ascites over a long period which was refractory to the treatment.[354]

Limitations

Patients with intra-abdominal LMs are treated with various modalities including sclerotherapy and surgical procedures. Modalities were combined in many cases, and complications are often reported as those of entire treatment without more detail information about those associated with individual treatment.

<Summary>

For answering the CQ, “What kinds of complications are associated with treatments for intra-abdominal LMs?”, no literature with a high level of evidence was found, but foreseeable complications could be listed from many case reports. Bowel obstruction, hemorrhage, pain, hematuria, and chylous ascites were reported as complications of sclerotherapy. Serious conditions, such as occlusion of the inferior vena cava and massive resection of the intestine, as well as common complications, such as wound infection, bowel obstruction, hemorrhage and chylous ascites were reported as complications after surgical procedures.

Although the incidence and difference of complications in respect of the site and histological type are not shown in the literature, each patient with intra-abdominal LMs should be treated with sufficient evaluation of the site, size and symptoms. In addition, treatment must be implemented with sufficient understanding of the possible complications.

Thus, we propose “Complications associated with sclerotherapy for intra-abdominal LMs include bowel obstruction, hemorrhage, pain, hematuria, and chylous ascites. Operative treatment of the disease can be associated with serious complications such as occlusion of the inferior vena cava and massive resection of the intestine as well as more common, wound infection, bowel obstruction, hemorrhage and chylous ascites.” as a recommendation draft.

CQ29: What are effective treatments for LMs causing airway stenosis in the mediastinum?

Recommendation:

Sclerotherapy is effective for macrocystic lesions, and surgical resection is effective for microcystic lesions. However, as the complication rate is relatively high, treatments should be selected according to the condition of each case.

Strength of recommendation 2 (weak)

Evidence D (very weak)

Comments

[Process of preparation of recommendation]

Among LMs, those that may cause airway stenosis due to their sites are life-threatening. Lesions in the mediastinum cause respiratory disorders if they physically compress the trachea or bronchi and stenosis the airway or markedly protrude into the thoracic cavity and narrow it.

In such situations, aggressive and effective treatment is necessary, but the therapeutic approach must be selected carefully in consideration of the relationship of the lesion with the important organs around it such as the large cardiac vessels, mediastinal nerve, and thoracic duct. However, the judgment is often difficult in clinical settings.

Therefore, the CQ, “What are effective treatments for LMs causing airway stenosis in the mediastinum?” was formulated, and the presently available knowledge concerning matters including the risk of complications and prognosis of treatments, such as surgical resection and sclerotherapy, was summarized.

<Literature search and screening>

As a result of literature search, 134 papers in Japanese and 227 in English (226 from PubMed, 1 from Cochrane) were subjected to primary screening. Of these papers, 5 in Japanese and 16 in English were subjected to secondary screening concerning this CQ. Since they included none with a high level of evidence, such as a systematic review or RCT, and all were case series or case reports, the results and discussion in each case series were integrated.

<Review of observational studies (case series)>

By screening of the literature, the following means were found for the treatment of LMs in the mediastinum.

Therapeutic options are surgical resection, puncture and drainage, sclerotherapy (OK-432, bleomycin, ethiblock, anhydrous ethanol), internal treatments (Chinese herbal medicines such as *eppikajutsuto* and *ogikenchuto*), and no treatment. Of these approaches, surgical resection and sclerotherapy using OK-432 have been evaluated in a relatively large number of cases, and reports of other therapy had extremely limited number of cases, e.g., reports of only 1 case.

Results of review

Boardman et al. reported that, of the 97 patients with LMs of the head and neck region, surgical treatments were necessary in 6 of the 12 patients with mediastinal lesions, that complications of surgery occurred in 4 of the 6 patients, and that long-term nerve damage was observed in 3 of them. In addition, they reported that management by tracheotomy was necessary in 15% of all patients. Complete or nearly complete remission was observed in 92% of the patients, but they suggested that surgical treatments should be indicated only when there is airway obstruction or there is the risk of it, because surgical treatment of mediastinal lesions frequently induces complications.[357]

Park et al. reported that they surgically resected mediastinal LMs in 12 patients. Seven of them had dyspnea, and 3 were asymptomatic, but they were all judged to have indications for surgery due to symptoms or the tendency of the lesions to enlarge. A total of 5 recurrences were observed in 4 patients (33%) during a mean period of 3.6 years after the initial surgery, but all were remitted by re-resection. No perioperative death was observed, and, in a total of 25 cases including

past cases, the overall survival was not different compared with that in healthy individuals over a follow-up period of 11.5 years.[358]

Smith et al. performed local injection of OK-432 in 16 patients with mediastinal LMs and reported ≥60% regression of the lesion in 13 (81%). They also mentioned treatment responses according to the histological types and, by reporting responses (complete or nearly complete remission) in 94% of those with macrocystic lesions, 63% of those with mixed lesions, but 0% in those with microcystic lesions, suggested a macrocystic lesion to be a good indication for sclerotherapy using OK-432. Although not from the viewpoint of airway stenosis, they reported that treatment using OK-432 was more effective than surgical resection and less frequently caused serious complications.[301]

Limitations

There have been no papers that directly analyzed treatments effective for mediastinal lesions expected to cause airway stenosis, and many papers reported cases of mediastinal lesions that responded to treatments. Therefore, we simply extracted matters relevant to this CQ from these reports.

<Summary>

There was no literature with a high level of evidence concerning effective treatments for LMs in the mediastinum causing airway stenosis. A few case reports that referred to the effects of surgery and sclerotherapy were observed, but it was difficult to present objective and specific figures concerning their effectiveness or safety. However, according to the available information, it should be noted that favorable responses have been obtained by OK-432 local injection in macrocystic lesions and that complications due to surgical resection are likely to occur relatively frequently.

From these observations, we consider the following to be a therapeutic approach that can be proposed: “Sclerotherapy, such as that by local injection of OK-432, should be considered for macrocystic lesions, and, for lesions that are technically difficult to treat by sclerotherapy or microcystic lesions, surgical resection should be considered with attention to complications. In addition, it is necessary to pay attention to the appearance of respiratory disturbances before and after these treatments and to constantly evaluate indications for airway securing by intratracheal intubation or tracheostomy.” Therefore, at present, we recommend, “Sclerotherapy is effective for macrocystic lesions, and surgical resection is effective for microcystic lesions. However, as the complication rate is relatively high, treatments should be selected according to the condition of each case.”

CQ30: Should sclerotherapy be commenced in infancy for a patient with head and neck LMs affecting airway?

Recommendation:

In a patient with LMs around the airway, there is risk of presenting respiratory distress in infancy, while airway obstruction is likely to be exacerbated by sclerotherapy. Particularly, when risk of airway obstruction is judged to be high or when the patient has already presented symptoms, it is proposed to commence sclerotherapy with sufficient preparations including airway management.

| | |
|---|---|
| Strength of recommendation | 2 (weak) |
| Evidence | D (very weak) |

Comments

[Process of preparing recommendation]

LMs of the neck, which are located in an exposed part of the body, may cause cosmetic problems which are important, but airway obstruction can particularly be a serious problem in some cases.

Sclerotherapy, which is one of the major treatment modalities, is most effective in patients with cystic LMs, but swelling of the treated portion after the therapy is concerned to cause or exacerbate airway obstruction symptoms especially in neonates. The upper airway will become less vulnerable to obstruction because it becomes less frail and wider as patients grow and respiratory distress tends to be unlikely. Therefore, it is occasionally difficult to determine how a patient who does not present any obstructive symptom should be treated in infancy.

Thus, we evaluated this problem by formulating the CQ, “Should sclerotherapy be commenced in infancy for a patient with the neck LMs affecting airway?”

<Literature search and screening>

As a result of search, 86 papers in Japanese and 135 papers in English (130 from PubMed, 5 from Cochrane) were subjected to primary screening. Of these papers, 6 in Japanese and 20 in English were subjected to secondary screening concerning this CQ. They included 1 systematic review (SR), 1 RCT, 2 prospective studies (PS) and 1 retrospective cohort study, but all the others were case series or case reports. Therefore, the results and discussion, primarily, in these SR, RCT, PS, and retrospective cohort study, but also in other case series were integrated.

<Review of observational studies>

Literature concerning the effectiveness of sclerotherapy for head and neck LMs in infancy was reviewed from the viewpoints of responses (prognosis <survival rate or mortality>, size, symptoms, and cosmetic improvement) and complications.

Sclerosing agents used as keywords for the present literature search varied widely and included OK-432, bleomycin, ethanol, doxycycline, sodium tetradecyl sulfate (STS) and fibrin glue. No paper evaluated differences in effectiveness of various agents due to their ways of administrations for lesions around the neck affecting airway. Therefore, differences between agents were excluded from the evaluation of this CQ.

Results of review

(1) Responses

A. Prognosis (survival rate or mortality)

According to the SR by Adams et al., the mortality was 4.7% in 277 cases with head and neck LMs.[359] Since lesions around the airway were not the only target, and since sclerotherapy was not the only treatment modality, the paper has not quite rightly answered to the CQ. However, since patients who died were all before one year of age and their causes of death are considered to have been mostly airway problems, such as airway obstruction and aspiration due to vocal cord paralysis in 8, and as at least one patient is judged to have died due to complications of invasive treatment, the paper is considered to indicate the risk of this disorder during infancy.

B. Size

Many of the papers that referred to the size regression evaluated it by four categories; (1) excellent or complete (≥90% regression), (2) good or substantial (≥50% and <90% regression), (3) fair or intermediate (≥20% and <50% regression), (4) and poor or none (≤20% regression).

Ravindranathan et al. treated 5 patients (aged 4-19 months) of cervicofacial LMs by sclerotherapy using OK-432 (in addition to fibrovein in 2) and reported that the responses were good in 1 (20%) (cystic), partial in 1 (20%) (cavernous), and poor in 3 (60%) (2 with cavernous lesions

that required tracheotomy and 1 with cystic lesions in whom the condition improved to good after surgical resection). However, they did not mention the evaluation criteria for good, partial, and poor.[305]

According to the report of 8 cases with head and neck LMs by Leung et al., all patients underwent sclerotherapy, ≥50% regression was observed in all patients with complete regression in 2. However, the patient age varied from 2 months to 11 years, and the types of LMs were not mentioned.[360]

Ogawa et al. reported 9 patients who underwent OK-432 sclerotherapy for the neck LMs and evaluated it to be markedly effective in 8 (88.9%), in whom the lesions mostly disappeared, and effective in 1, who showed a ≥50% regression. Eight patients (including 5 preschoolers and toddlers, 2 school children, and 2 adults) in whom the treatment was markedly effective consisted of 1 with mixed and 7 with cystic lesions, and the one in whom the treatment was effective had a mixed type.[361]

Cahill et al. reported doxycycline sclerotherapy in 17 patients with head and neck LMs (cystic in 10, mixed in 7 (3 required tracheotomy)), and its size regression was reported to be >90% in 7 (41.2%) (cystic in 6, mixed in 1), 75-89% in 4 (23.5%) (cystic in 2, mixed in 2), 51-74% in 4 (23.5%) (cystic in 1, mixed in 3), and 25-50% in 2 (11.8%) (mixed in 2).[314]

Nehra et al. reported doxycycline sclerotherapy in 11 patients with head and neck LMs (cystic in 7, mixed in 4; aged 2 days-21 months) (later combined with surgical resection in 3). The treatment results were excellent in 5 (45.5% of all patients) and satisfactory in 2 (18.2% of all patients) among 7 patients with cystic lesions but poor in all 4 patients with mixed type lesions (36.4% of all patients). Particularly, 3 of the 4 patients with mixed type lesions required tracheal intubation shortly after birth and underwent sclerotherapy while intubated, but the effects were poor in all of them. Surgical resection was added in one and is under consideration in another.[310]

C. Symptoms

According to Ravindranathan et al. who reported 5 patients with cervicofacial LMs (aged 4-19 months) treated with sclerotherapy using OK-432 (in addition to fibrovein in 2), 4 (80%) exhibited symptoms of airway obstruction before treatment. Symptoms included dysphagia in 2 (20%) and dyspnea (including croup-like symptoms) in 4 (80%) (some both). Symptoms were alleviated by sclerotherapy in 2 out of 4 (40%) (cystic 1, cavernous 1), but tracheotomy was necessary in the remaining 2 (40%) (cavernous in both) without improvement.[305]

In the report of 8 patients with head and neck LMs and 5 patients with VMs (aged 2 months-11 years) by Leung et al., their symptoms noted before treatment were mass or swelling (10 patients (77%)), pain after hemorrhage (2 patients (15%)), skin discoloration (blue) (1 patient (8%)), obstructive airway symptoms (6 patients (46%)), and swallowing difficulty (1 patient, (8%)). All symptoms were alleviated by sclerotherapy (doxycycline for LMs, STS foam for VMs).[360]

Arimoto et al. reported a patient with cystic LM in the neck presented 3 months after birth. The patient presented respiratory distress at the age of 10 months due to enlargement of the LM following upper respiratory infection. While left vocal cord fixation due to the mass was confirmed by ultrasonography before treatment, aspiration of the cyst and steroid administration resulted in opening of the glottic area and regression of the mass with relief of wheezing and distress. Since they underwent sclerotherapy 2 months after the disappearance of symptoms, aspiration of internal fluid and steroid administration rather than sclerotherapy were directly effective for the alleviation of symptoms.[362]

Kitagawa et al. reported a patient with giant LM of the neck which had been prenatally diagnosed and was treated under ex utero intrapartum treatment (EXIT) by tracheal intubation after aspiration of the cyst. The lesion was reported to be refractive to subsequent sclerotherapy and

tracheotomy was eventually needed.[363]

Nehra et al. reported that, among 11 patients with head and neck LMs (cystic type in 7 and mixed type of cystic + cavernous in 4; aged 2 days-21 months), 3 out of 4 with mixed LMs presented respiratory distress soon after birth and were managed by intubation, but that all could be extubated after sclerotherapy using doxycycline (1-3 times, median: 1.6 times).[310]

D. Cosmetic improvements

No paper has reported cosmetic results in detail. Only sporadically they mentioned about surgery for redundant skin after regression of cystic lesions by sclerotherapy.

(4) Complications

Complications associated with treatment for LMs around the airway have been reported in many papers. They include temporary conditions caused by sclerotherapy such as fever,[291, 302, 311, 361, 364-370] local swelling[302, 311, 364, 366, 367, 369, 370] pain,[287, 311, 361, 366, 369-371] hemorrhage into the cyst,[287, 302, 311, 367] and infection.[287, 291, 302, 309, 311, 359, 364, 371] There also reported complications as the effects of treatment for head and neck lesions such as respiratory distress due to airway obstruction,[291, 302, 305, 311, 361, 364, 365] as well as nerve palsy.[287, 291, 311, 359, 364]

According to a systematic review about head and neck LMs by Adams et al., both nerve damage due to sclerotherapy and post-therapeutic infection were reported in 1 (0.8%) out of 123 patients. Since nerve damage and infection after surgery were observed in 12 (10.2%) and 7 (5.9%) out of 118 patients, respectively, the complication rate is would to be lower by sclerotherapy than by surgery.[359]

Ogawa et al. reported a 1-year-and-5-month-old patient who developed airway edema after OK-432 sclerotherapy for the cystic neck LM and necessitated tracheal intubation for 3 days and

cautioned against sclerotherapy for LMs around the airway in young children (particularly, those less than 2 years old).[361]

Kudo et al. also reported 2 patients aged 11 months and 1 year and 11 months who were treated with OK-432 sclerotherapy intubated in advance for fear of airway obstruction due to post-therapeutic swelling.[368] Tomemori et al.[372] also cautioned against sclerotherapy for LMs in children aged less than 2 years likewise the report by Ogawa et al.[361]

On the other hand, Kudo et al. reported 2 cases whose neck LMs having been enlarged rapidly after suffering from measles or upper respiratory tract infection (URTI).[368] Arimoto et al. also reported a patient with cystic LM of the neck presented 3 months after birth who, who developed dyspnea due to enlargement of the lesion after URTI at 10 months and was about to be intubated.[362]

Regarding complications due to sclerosing agents, Cahill et al. reported those by doxycycline, STS and absolute ethanol. They reported delayed complications, such as Horner's syndrome, transient left lip weakness, right facial nerve palsy, and transient left hemidiaphragm paralysis, in addition to peri-procedural complications such as hemolytic anemia after doxycycline injection in 2 patients, hypoglycemic and metabolic acidosis in 3 neonates, transient hypotension during absolute alcohol instillation and self-limiting skin excoriation secondary to peri-catheter leakage of doxycycline.[314] Other reported complications include permanent vocal cord paralysis after local ethanol injection,[373] serious complications after OK-432 injection such as death due to pulmonary embolism,[374] deaths due to pulmonary complications after treatment using bleomycin[375, 376] and leukocytopenia due to bleomycin.[367]

Limitations

There are few papers that analyzed only LMs around the cervical airway. Most papers included lesions involving not only the neck but also the craniofacial and other parts of the body and

reported LMs with different properties such as cystic and mixed types. In addition, definition of cavernous lesions and methods of sclerotherapy (injection techniques, number of injections, etc.) were not similar between papers, and differences in these backgrounds must be taken into consideration to evaluate effectiveness of sclerotherapy.

<Summary>

The CQ, “Should sclerotherapy be commenced in infancy for a patient with head and neck LMs affecting airway?”, was evaluated from the viewpoints of responses (prognosis (survival rate or mortality), decrease in size, symptoms, cosmetic improvements) and complications. Since there have been some reports warning risk of presenting respiratory distress due to LMs around the airway in infant, and therapeutic intervention is necessary even in infants when the risk is high or they have already presented symptoms. Such intervention is made by sclerotherapy or surgery, and as surgical resection is associated with high risk of more serious complications than sclerotherapy, intervention by less invasive sclerotherapy is recommended. Sclerotherapy is considered to be very effective because of high regression rate of the lesion and symptom/function-improving effect. However, its effect varies depending on the disease type, somewhat less effective in the cavernous and mixed types than in the cystic type. Furthermore, when it was applied to the lesion around the airway, it may be associated with risk of exacerbation of airway obstruction symptoms due to reactive enlargement of the lesion. Thus, we formulated the recommendation, “In LMs around the airway, there is the risk of respiratory disturbances from infancy, but airway stenosis is likely to be exacerbated by sclerotherapy. Particularly, when the risk of airway stenosis is judged to be high or when symptoms have appeared, it is proposed to perform sclerotherapy with sufficient preparations including airway securing.”

CQ31: Is surgical resection effective for LMs of the tongue?

Recommendation:

Surgical resection is effective for reducing the size of the lesion and alleviating symptoms and functional impairment. However, total resection is often difficult, and careful decision is required in consideration of the possibility of complications and recurrence.

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| Strength of recommendation | 2 (weak) |
| Evidence | D (very weak) |

Comments

[Process of preparation of recommendation]

While the tongue is one of the frequent sites of LMs, the lesion is often distributed widely over the neck rather than is localized in the tongue. LMs of the tongue not only cause cosmetic problems, such as protrusion from the mouth and bleeding, but also readily occupy the oropharyngeal cavity and cause functional problems such as disorder of mouth closing, difficulty in speaking, respiratory disturbances, and impairment of oral food intake. These conditions are treated at departments including plastic surgery, oral surgery, otorhinolaryngology, and pediatric surgery. LMs of the tongue are treated by surgical resection or sclerotherapy, but comprehensive evaluation of the condition of individual cases including the distribution of the lesion in the tongue, involvement of other areas and cyst components, and vascular distribution in addition to general information, such as the risk of complications and recurrence in each treatment, is necessary.

Therefore, the CQ, “Is surgical resection effective for LMs of the tongue?” was formulated, and the present knowledge about the effectiveness of surgical resection of the lesion, particularly, by partial glossectomy was summarized.

<Literature search and screening>

As a result of search, 29 papers in Japanese and 76 papers in English (75 from PubMed, 1 from Cochrane) were subjected to primary screening. Of these papers, 2 in Japanese and 10 in English were subjected to secondary screening concerning this CQ. They included 1 retrospective cohort study, but most other papers were case series or case reports. Consequently, in the evaluation of this CQ, the results and discussion of the cohort study and each case series were integrated.

<Review of observational studies (case series)>

The effectiveness of surgical resection of LMs of the tongue was evaluated from the viewpoints of resectability of the lesion, symptoms, function, and cosmetic improvements as elements of responses as well as complications and recurrence.

Results of review

(1) Responses

A. Resectability of the lesion

Twenty-four cases of tongue lesions treated by surgical resection alone were reported in 4 papers. Catalfamo et al. performed surgical resection of localized masses including normal structures with a margin of 1 cm in the horizontal direction and reported that the size of tongue lesions could be reduced in 8 (88.9%) of the 9 patients.[377]

Concerning large lesions impossible to resect totally, Boardman et al. reported 13 cases of partial surgical resection, but multiple operations were often necessary to reduce lesion size.[357] A total of 2 case have been reported,[378, 379] and the lesion size could be reduced in both. Although differences were observed in re-enlargement after surgery, they are discussed in detail in “(2)

Complications”.

In 1 case report, sclerotherapy was performed 15 times, but the lesion size could not be reduced, and surgical resection was selected, eventually resulting in a favorable outcome without recurrence.[380]

According to a report of 89 cases of head and neck LMs by Lei et al., the outcome was excellent in 73 (82%) and good in 16 (18%) although it was not a report of cases of tongue lesions alone. They included 43 cases of tongue lesions.[290]

In addition, a few papers that suggested the effectiveness of combinations of surgical resection with sclerotherapy and laser therapy were observed.[381-384] Wiegand et al. classified the disease into 4 stages according to the area of involvement and reported that the stage can be a prognostic factor.[382] Surgery was effective, and complications were rare, when the lesion was localized in the superficial layer and part of the muscle layer. Surgical resection can also be effective, but complete resection is difficult, when the lesion extends over the entire muscle layer or to the tongue base and neck. Therefore, partial resection is often repeated and combined with laser therapy and sclerotherapy, but the recurrence is observed very frequently, and the results did not contradict the reports mentioned below in the section of the recurrence rate.[290, 357]

B. Symptoms

A wide variety of symptoms have been reported depending on the site of the mass, and they include tongue discomfort, bleeding, pain, and difficulty in oral feeding.[385] Roy et al. reported that bleeding from the tongue surface, pain, and eating difficulty were alleviated by cauterization.[386]

C. Functions

In most patients who exhibited functional impairment, the lesions were so extended that

they were no longer indications for one-time surgical resection. Large masses located at sites such as the tongue base cause respiratory disturbances, swallowing disorders, and difficulty in speech. According to the report by Azizkhan et al.,[384] oral intake of normally cooked food became possible in 14, and normal vocalization became possible in 8, of the 21 patients with tongue base lesions. In addition, 5 of the 17 patients who needed tracheotomy could be weaned.

D. Cosmetic improvements

Objective evaluation of cosmetic effects is also difficult.

Azizkhan et al. reported that, of the 20 patients, excluding 1 with severe deformity who died, deformity of structures around the tongue, such as the mandible and maxilla, was mild in 6, moderate in 5, and severe in 9.[384] There have been a few reports that cosmetic improvements were also observed in patients who showed a reduction of the tongue size by surgical resection, but objective evaluation is insufficient.

(2) Complications

Although the properties of the lesions are unclear in some papers, facial nerve paralysis, vagus nerve paralysis, infection, hematoma, seroma, salivary leakage, ruptured suture, and skin flap necrosis have been reported as complications of the facial region. There have also been reports of temporary complications such as pain and hemorrhage.

(3) Recurrence

There have been a few postoperative evaluations reporting that no reactivation that clinically required treatment was observed. Lei et al. reported greater details: Recurrence was observed in 21 (23.6%) of 89 patients and was more frequent in those aged less than 1 year, those

with lesions in the oral cavity/face, those with lesions at 3 or more sites, and those with microcystic lesions.[290] According to Boardman et al., LMs of the tongue recurred in 12 (48%) of 28 patients, more often than other head and neck lesions.[357] As factors related to this more frequent recurrence of lingual LMs, more frequent involvement of other regions, such as the floor of mouth, and a high percentage of microcystic lesions (70%) have been suggested. Of the 2 cases treated by surgical resection alone, 1 who underwent resection of the middle part of the tongue showed no re-enlargement for 1 year or longer after surgery,[378] but surgery was repeated 3 times in the 1 who underwent marginal resection.[379] This patient who underwent repeated resections also showed no re-enlargement although the time of the last resection is unclear.

Limitations

In some papers, surgical resection was combined with other treatments,[380-384, 386] lesions in other areas such as the neck were included,[290] and the lesion types were unknown. The lack of standardization of subjects and uniformity of the definition or time of recurrence must be considered in the evaluation of the effectiveness of surgical resection.

<Summary>

Many papers suggest that surgical resection is effective for reducing the size of lingual LMs. However, in patients with large lesions, lesions extending to structures other than the tongue, and microcystic lesions, multiple resections or combination of resection with other treatments such as sclerotherapy and laser therapy were necessary, and the recurrence rate tended to be higher. While a few papers referred to symptoms, functional outcome, and cosmetic improvements, none showed a high level of evidence, and the evidence was insufficient for general discussion of the effectiveness of surgical resection.

Therefore, concerning the effectiveness of surgical resection for LMs of the tongue, “Surgical resection is effective for reducing the size of the lesion and alleviating symptoms and functional impairment. However, total resection is often difficult depending on the distribution of the lesion, and careful decision is required in consideration of the possibility of complications and recurrence.” was proposed as a draft recommendation.

CQ32: Is aggressive surgical intervention effective for chylous pleural effusion in the neonatal period?

Recommendation:

For chylous pleural effusion refractory to conservative treatments, surgical procedures, such as pleurodesis, ligation of the thoracic duct, and pleuroperitoneal shunting, may be effective.

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| Strength of recommendation | 2 (weak) |
| Evidence | D (very weak) |

Comments

[Process of determining recommendation]

Primary chylous pleural effusion during the neonatal period is often refractory and can be fatal. Thoracic drainage is performed for respiratory insufficiency due to accumulation of pleural effusion, followed by conservative treatments, such as nutritional therapy, steroid, and octreotide therapy, conducted primarily by neonatologist until resolution of chylous pleural effusion.

In refractory cases that do not respond to these conservative therapies, surgical intervention, such as ligation of the thoracic duct and pleurodesis, may be performed. However, no sufficient consensus has been obtained concerning their effects. To evaluate problems, such as at what point

surgical intervention should be made and whether aggressive surgical intervention is effective for such a condition, the CQ, “Is aggressive surgical intervention effective for chylous pleural effusion in the neonatal period?”, was formulated, and the knowledge available at present was summarized.

<Literature search and screening>

As a result of search, 98 papers in Japanese and 264 papers in English (262 from PubMed, 2 from Cochrane) were subjected to primary screening. Of these papers, 8 in Japanese and 9 in English were subjected to secondary screening concerning this CQ. They included none with a high level of evidence, such as a systematic review or RCT that evaluated surgical treatment, and all papers were case series or case reports. Consequently, the results and discussion in each of the case series judged to be useful for the preparation of the draft recommendation were integrated although they were weak as the evidence for the evaluation of this CQ.

<Review of observational studies (case series)>

The literature concerning the effectiveness of surgical treatment for chylous pleural effusion in the neonatal period was reviewed from the viewpoints of responses and complications.

Results of review

(1) Responses

Surgical treatment for neonatal chylothorax is performed in patients who respond insufficiently even to thoracic drainage in addition to nutritional therapy using MCT (middle-chain triglyceride) milk or total parenteral nutrition or internal treatment such as octreotide administration.

The methods for surgical intervention found by the present literature review included ligation of the thoracic duct and pleuroperitoneal shunt as well as pleurodesis with OK-432

administration, intrathoracic infusion of fibrin, and povidone-iodine administration, and some patients diagnosed in utero underwent pleuro-amniotic shunting. Cases in which mildly invasive treatments, such as thoracoscopic ligation of the thoracic duct and intrathoracic fibrin application, have been reported in addition to those who underwent thoracic duct ligation by thoracotomy.

Treatments that were performed before surgery and their periods were not uniform. In addition, since there are cases that developed chylous pleural effusion after surgery and those of congenital chylothorax, the diversity of the patient background must be taken into consideration in the efficacy evaluation.

Among the surgically treated cases, those in whom chylous plural effusion disappeared, respiratory symptoms were alleviated, and weaning from the respirator became possible have been reported.[387, 388] In addition, the absence of recurrence or reactivation is considered to be a point. [387-390] There were reports that chylous pleural effusion after thoracic surgery was resolved by drainage alone. Cleveland et al. considered conservative treatments, such as total parenteral nutrition (TPN), octreotide, and diuretic administration, to be the best and, observing that, of the poor responders, the mortality was 80% in 5 continued to be managed by conservative treatments but 0% in 4 who underwent additional surgery, reported that surgical treatment contributed to the reduction of the mortality.[391] According to the guidelines for the treatment of chylous thoracic effusion by Buttiker et al.,[392] conservative treatment is worth continuing for about 3 weeks but should be abandoned thereafter because of the risk of nutritional disturbance, increased susceptibility to infection, and liver disorders. However, Kaji et al. reported that it is difficult to set a clear period of conservative therapy, because the effectiveness and success rate of surgical treatment are unclear.[393]

(2) Complications

As complications due to sclerosing agents, fever and increased inflammatory reaction due to

the administration of OK-432 as well as pulmonary abscess and temporary flaccidity and protrusion of the upper abdominal region considered to have been due to intercostal nerve damage have been reported. While chyle leakage in the abdominal cavity was noted in a patient who underwent pleuroperitoneal shunting, there were no reports of fatal complications.

Limitations

Surgical treatment was performed in most reported cases when responses to conservative therapy were not obtained. Therefore, it must be assumed that the results of evaluation of this CQ are based on data concerning the effectiveness of surgery performed with conservative therapy.

<Summary>

The literature was reviewed concerning the effectiveness of aggressive surgical intervention for neonatal chylous thoracic effusion from the viewpoints of responses and complications, but no objective study with a high level of evidence was found. In most reported cases, surgical treatment was performed when responses to conservative treatments were poor. Therefore, it is difficult to compare surgery with other therapies, and the evaluation of the period of conservative treatment before surgery remains insufficient. However, there was a paper that proposed surgical intervention after attempting conservative treatments for 3 weeks as a standard.

Thus, surgical intervention for neonatal chylous pleural effusion is characterized at present as an approach that may be effective but should be evaluated when the condition is not improved by other treatments, and “Surgical procedures, such as pleurodesis, ligation of the thoracic duct, and pleuroperitoneal shunting, may be effective for chylous pleural effusion refractory to conservative treatments.” is proposed as a draft recommendation.

CQ33: What are treatments effective for refractory chylous pleural, and pericardial effusion and respiratory disturbances of the patients with generalized lymphatic anomaly (GLA) and Gorham-Stout disease (GSD)?

Recommendation:

While treatments including surgery, sclerotherapy, radiotherapy, nutritional therapy, and drug therapy are conducted, there is presently no effective treatment with a high level of evidence. Treatments should be selected in consideration of complications and adverse effects according to individual symptoms.

| | |
|---|---|
| Strength of recommendation | 2 (weak) |
| Evidence | D (very weak) |

Comments

[Processof preparation of recommendation]

GLA and GSD are refractory diseases that cause a wide variety of symptoms in the entire body and are difficult to diagnose and treat. The investigation by the Health and Labour Sciences Research group (Ozeki group) carried out by 2013 showed that the mortality is particularly high when the patients had thoracic lesions.

Among the wide variety of thoracic symptoms, chylous pleural effusion/pericardial effusion are often refractory and occasionally fatal. While information about the disease is extremely limited because of its rareness, case reports are being globally accumulated as chronic cases are managed on an outpatient basis, and as severe cases are treated intensively.

Presently, no radical treatment for these refractory diseases is known, but the CQ, “What are treatments effective for refractory chylous pleural, and pericardial effusion and respiratory

disturbances of the patients with GLA and GSD?" was formulated to compile the knowledge about what treatments are effective as it is a problem of clinical importance.

<Literature search and screening>

As a result of search, 208 papers in Japanese and 617 papers in English (598 from PubMed, 19 from Cochrane) were subjected to primary screening. Of these papers, 2 in Japanese and 25 in English were subjected to secondary screening concerning CQ 37. They included no studies with a high level of evidence, such as a systematic review and RCT, and all were reports of 1-2 cases. Therefore, the evaluation of this CQ was performed by integrating the results and discussion in case series judged to be useful for the preparation of the draft recommendation despite the lack of evidence.

<Review of observational studies (case series)>

The effectiveness of various treatments for refractory GLA and GSD was evaluated according to the prognosis and the presence or absence of improvement in imaging findings, improvement in symptoms, improvement in airway stenosis, enlargement of the lesion, regression, treatment-related complications, recurrence, and reactivation.

Conditions of patients

The cause of chylous pleural and pericardial effusion is lymphorrhea from lymphatic vessel tissue lesions that have primarily invaded the mediastinum and pleura, and lymphorrhea from osteolytic lesions of the ribs and vertebrae was also observed. Respiratory disturbances were caused by pleural effusion, chylous pleural effusion, pericardial effusion, and direct invasion of the mediastinum and lungs.

Results of review

As surgical treatments for chylous pleural effusion, procedures, such as thoracentesis, thoracic drainage, ligation of the thoracic duct, and pleural decortication, have been performed, and local lesions were surgically resected. In most cases, thoracentesis and thoracic drainage were performed, but chyle leakage was not resolved. As for complications, there were cases that developed hypovolemic shock and required blood transfusion and catecholamine administration or supplementation of albumin, immunoglobulin, and clotting factors.[394-396] While chylous pleural effusion could be controlled in some patients who underwent ligation of the thoracic duct,[396-407] the treatment was performed in combination with other surgical procedure or radiotherapy in all cases.[399, 401, 407] There was 1 case that showed improvement in respiratory disturbance.[405] As complications of ligation of the thoracic duct, splenomegaly and lymphorrhea[404] and left-sided pleural effusion[396, 404] have been reported. In the patients who showed marked improvements in chylous pleural effusion[394, 404, 407] after pleural decortication,[394, 395, 400, 402-404, 407, 408] the procedure was performed in combination with other surgical treatments or sclerotherapy, and there was no mention about complications. There were cases that showed marked improvements in chylous pleural effusion[395, 399, 404, 407] among those who underwent surgical resection of local lesions including splenectomy,[2,3,6,11,14,16-18) 395, 396, 399, 404, 407, 409-411] but the procedure was performed in combination with other surgical treatments in most of them. Hemorrhage was reported as a complication.[409] Among other treatments, pleuroperitoneal shunt[402] and lung transplantation[412] were performed, and alleviation of respiratory disturbance was noted in the patient who underwent lung transplantation.

As a surgical treatment for pericardial effusion, pericardiocentesis was performed,[395, 413-415] and pericardial fenestration was performed when pericardial effusion could not be controlled by

pericariocentesis.[395, 415] There was no mention about complications.

As sclerotherapy, pleurodesis was performed using OK-432, talc, and minocycline.[394, 396-398, 403, 407, 410, 415-417] There were cases that responded markedly to sclerotherapy alone and sclerotherapy combined with surgical procedures such as pleural decortication or local radiotherapy. There was no mention about complications of sclerotherapy.

There have also been reports on local (e.g., lesion area, thoracic duct region) and thoracic radiotherapy for chylous pleural effusion and local lesions,[398, 399, 401-403, 409-411, 414, 415, 417-419] and marked responses of chylous pleural effusion and responses of respiratory symptoms were noted, but other treatments were performed concomitantly in some patients. Radiation pneumonitis has been reported as a complication.[415]

Concerning nutritional therapy, fasting, high-calorie infusion, and medium chain triglyceride (MCT) diet have been performed alone or in combinations, but few cases that showed alleviation of chylous pleural effusion were observed.[394, 395, 397-399, 402, 404, 407, 420]

For drug therapy against chylous pleural effusion, drugs including interferon α, propranolol, anticancer agents (e.g., vincristine), bisphosphonate, octreotide, steroid, sirolimus, and low-molecular-weight heparin were used. Interferon α was used most frequently,[394-397, 399, 400, 402, 414, 420] and marked improvement in chylothorax was reported in 5 cases. Of these cases, interferon α was used with propranolol in 1[394] and with low-molecular-weight heparin and local radiotherapy (15 Gy) in 1.[399] As for complications of drug therapy using interferon α, there were reports of fever, nausea, and headache[420] and thrombocytopenia and hepatic toxicity.[396] There was no report of improvement in chylous pleural effusion by the use of steroid[394, 398, 402, 414] or octreotide[394, 396, 397, 399, 402, 404] alone. Concerning other drug therapies, only a few cases have been reported with no improvement in chylous pleural effusion. One case that showed regression of mediastinal invasion of GLA and alleviation of respiratory disturbance by sirolimus treatment has been reported,[413] and hypertension

was noted as a complication. In drug therapy for pericardial effusion, diuretics were used for conservative therapy.[399]

Limitations

Although cases that responded to various therapies have been reported, treatments are often performed in combinations, and the evaluation of the effectiveness of each treatment alone is difficult at this point.

<Summary>

Treatments effective for GLA and GSD presenting with refractory chylous pleural effusion, pericardial effusion, and respiratory disturbances were evaluated by a review of the literature, which was primarily case reports. Various treatments, such as surgery, sclerotherapy, radiotherapy, nutritional therapy, and drug therapy, have been performed, but, there was no study with a sufficient number of cases and a high level of evidence because of the rareness of the disease and diversity of symptoms. Although cases that responded to various treatments have been reported, treatments are frequently performed in combinations, and the evaluation of the effectiveness of individual therapies is difficult at present. Sirolimus (a mTOR inhibitor) is considered promising as a drug for this disease, and some clinical trials are currently under way in Japan and abroad.

In actual clinical situations, these diseases are not recognized as indications of various drug therapies by the Japanese health insurance system, and the therapeutic effects of other treatments are also uncertain. Therefore, the above treatments cannot be recommended, but we propose that treatments “should be selected in consideration of complications and adverse effects according to individual symptoms.” It is necessary to evaluate the invasiveness, complications, adverse effects, etc. and select the treatments judged to be appropriate for each case.

Conclusion

The practice guidelines for vascular anomalies have been prepared as the evidence-based guidelines for the management of vascular anomalies.

Acknowledgement

This work was supported by Grants-in Aid from the Research Committee of Intractable Vascular Anomalies, Research on Policy Planning and Evaluation for Rare and Intractable Diseases, Health, Labour and Welfare Sciences Research Grants, the Ministry of Health, Labour and Welfare, Japan. We thank all members of the systematic review team as follows. Tomoko Izaki, Ryohei Ishiura, Yohei Iwata, Tatsuo Ueda, Naoki Ohkura, Sachiyo Ohsawa, Jun Ohtaka, Kuniaki Ohara, Shinya Ogishima, Takuro Kazama, Motoi Kato, Takahide Kaneko, Motohiro Kano, Tamihiro Kawakami, Tatsuki Kono, Eisuke Shibata, Syunsuke Sugawara, Yousuke Suyama, Kazuhiro Takahashi, Yuichi Takama, Takaya Takeguchi, Kensuke Tashiro, Masashi Tamura, Atsushi Tamura, Masato Tsuchiya, Kyoichi Deie, Toshihide Tokuda, Asami Tozawa, Fumio Nagai, Michiko Nagahama, Yasuhiro Nakamura, Akifumi Nozawa, Naoki Hashizume, Takuya Hara, Koji Higuchi, Masahito Hibi, Takaya Fukumoto, Shinji Fujizuka, Megumi Furuya, Seiji Hobara, Kyoko Hoshino, Tomohiro Hori, Takanobu Maekawa, Junko Miyata, Kenji Murakami, Kiichiro Yaguchi, Daisuke Yasui, Kentaro Yamada, Yohei Yamada, Yuki Yamamoto, and Azusa Watanabe.

**Table and Figure**

Table 1: Recommendation Grade and Definition of the Strength of Body of Evidence in Evaluation of Systematic Review

| |
|---|
| Recommendation grade |
| 1 strongly recommended |
| 2 weakly recommended (suggested) |
| Definition of the Strength of Body of Evidence in Evaluation of Systematic Review |

A (strong) : strongly confident of the estimate of effect

B (moderate) : moderately confident of the estimate of effect

C (weak) : limited confidence of the estimate of effect

D (very weak) : very little confident of the estimate of effect

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Figure 1: Reports of laser therapy for hemangiomas/vascular malformations (primarily venous) in various periods and types of laser used in the reports

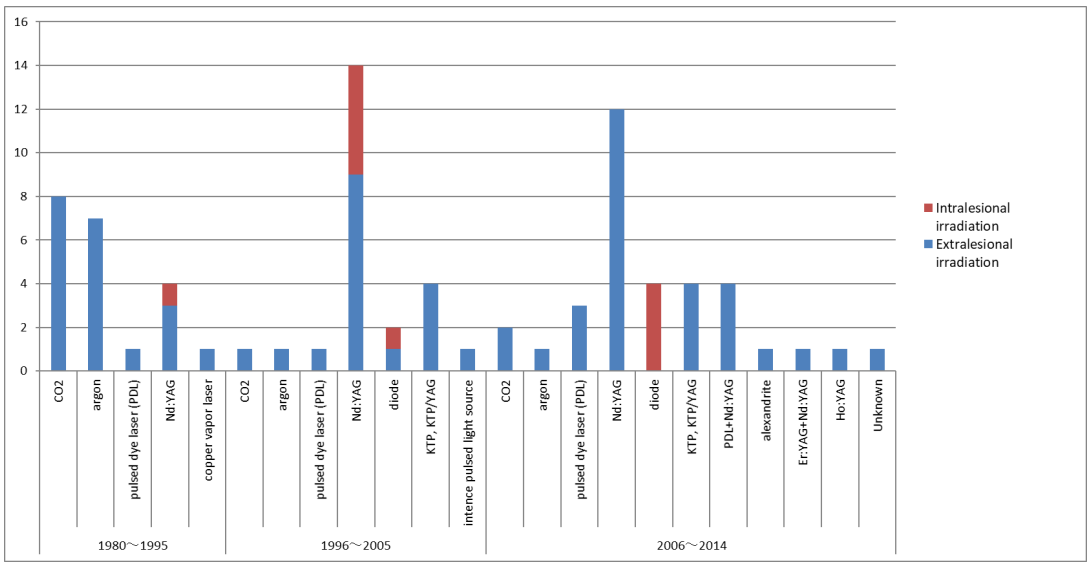


Figure legends

Figure 1

Notes

CO2; 10 of 11 reports recommend the use for surgical resection.

Argon; There are 4 reports of mixed treatments for capillary malformations and VMs.

Nd:YAG; There are 12 reports of its use in combination therapy with surgery, sclerotherapy, or other lasers.

Alexandrite; There is only 1 report summarizing cases treated with alexandrite in combination therapy with other lasers.

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平成　31　年　3　月　29　日

国立保健医療科学院長　　殿

機関名　福岡大学

所属研究機関長　職　名　学長

氏　名　山口　政俊　　印

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　難治性血管腫・血管奇形・リンパ管腫・リンパ管腫症および関連疾患についての調査研究

３．研究者名　　（所属部局・職名）　医学部・教授

（氏名・フリガナ）　秋田定伯・アキタ　サダノリ

４．倫理審査の状況

| | 該当性の有無 | 左記で該当がある場合のみ記入（※1） | | |
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| | 有　無 | 審査済み | 審査した機関 | 未審査（※2） |
| ヒトゲノム・遺伝子解析研究に関する倫理指針 | □　■ | □ | | □ |
| 遺伝子治療等臨床研究に関する指針 | □　■ | □ | | □ |
| 人を対象とする医学系研究に関する倫理指針（※3） | ■　□ | ■ | 福岡大学 | □ |
| 厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針 | □　■ | □ | | □ |
| その他、該当する倫理指針があれば記入すること（指針の名称：　　） | □　■ | □ | | □ |

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

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６．利益相反の管理

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| 当研究機関におけるＣＯＩの管理に関する規定の策定 | 有 ■　無 □（無の場合はその理由：　　） |
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（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

平成31年　3月　31日

国立保健医療科学院長　殿

機関名　国家公務員共済組合連合会　斗南病院

所属研究機関長　職　名　病院長

氏　名　奥　芝　俊　一　印

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

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３．研究者名　（所属部局・職名）　血管腫・脈管奇形センター・　血管腫・脈管奇形センター長

（氏名・フリガナ）　佐々木　了（ササキ　サトル）

４．倫理審査の状況

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２０１９年４月１日

国立保健医療科学院長　殿

機関名　聖マリアンナ医科大学

所属研究機関長　職　名　学長

氏　名　尾崎　承一　　印

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

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３．研究者名　（所属部局・職名）医学部・教授

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４．倫理審査の状況

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| 当研究機関におけるＣＯＩ委員会設置の有無 | 有 ■　無 □（無の場合は委託先機関：　　） |
| 当研究に係るＣＯＩについての報告・審査の有無 | 有 ■　無 □（無の場合はその理由：　　） |
| 当研究に係るＣＯＩについての指導・管理の有無 | 有 □　無 ■（有の場合はその内容：　　） |

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

平成３１年３月３１日

国立保健医療科学院長　殿

機関名　独立行政法人労働者健康安全機構
所属研究機関長　職　名　千葉労災病院
氏　名　院長 河野陽一　印

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　難治性血管腫・血管奇形・リンパ管腫・リンパ管腫症および関連疾患についての調査研究

３．研究者名　（所属部局・職名）　千葉労災病院　形成外科部長

（氏名・フリガナ）　力久　直昭・リキヒサ　ナオアキ

４．倫理審査の状況

| | 該当性の有無 | 左記で該当がある場合のみ記入（※1） | | |
|---|---|---|---|---|
| | 有　無 | 審査済み | 審査した機関 | 未審査（※2） |
| ヒトゲノム・遺伝子解析研究に関する倫理指針 | □　■ | □ | 該当しないため | ■ |
| 遺伝子治療等臨床研究に関する指針 | □　■ | □ | 該当しないため | ■ |
| 人を対象とする医学系研究に関する倫理指針（※3） | ■　□ | ■ | 千葉労災病院 | □ |
| 厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針 | □　■ | □ | 該当しないため | ■ |
| その他、該当する倫理指針があれば記入すること（指針の名称：　） | □　■ | □ | 該当しないため | ■ |

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

| | |
|---|---|
| 研究倫理教育の受講状況 | 受講 ■　未受講 □ |

６．利益相反の管理

| | |
|---|---|
| 当研究機関におけるＣＯＩの管理に関する規定の策定 | 有 ■　無 □（無の場合はその理由：　） |
| 当研究機関におけるＣＯＩ委員会設置の有無 | 有 ■　無 □（無の場合は委託先機関：　） |
| 当研究に係るＣＯＩについての報告・審査の有無 | 有 ■　無 □（無の場合はその理由：　） |
| 当研究に係るＣＯＩについての指導・管理の有無 | 有 □　無 ■（有の場合はその内容：　） |

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

平成31年2月27日

国立保健医療科学院長 殿

機関名　大阪大学大学院医学系研究科

所属研究機関長　職　名　医学系研究科長

氏　名　金田　安史　印

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　難治性血管腫・血管奇形・リンパ管腫・リンパ管腫症および関連疾患についての調査研究

３．研究者名　（所属部局・職名）大学院医学系研究科・准教授

（氏名・フリガナ）大須賀　慶悟・オオスガ　ケイゴ

４．倫理審査の状況

| | 該当性の有無 | 左記で該当がある場合のみ記入（※1） | | |
|---|---|---|---|---|
| | 有　無 | 審査済み | 審査した機関 | 未審査（※2） |
| ヒトゲノム・遺伝子解析研究に関する倫理指針 | □　■ | □ | | □ |
| 遺伝子治療等臨床研究に関する指針 | □　■ | □ | | □ |
| 人を対象とする医学系研究に関する倫理指針（※3） | □　■ | □ | | □ |
| 厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針 | □　■ | □ | | □ |
| その他、該当する倫理指針があれば記入すること（指針の名称：　） | □　■ | □ | | □ |

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。

（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

| | |
|---|---|
| 研究倫理教育の受講状況 | 受講 ■　未受講 □ |

６．利益相反の管理

| | |
|---|---|
| 当研究機関におけるＣＯＩの管理に関する規定の策定 | 有 ■　無 □（無の場合はその理由：　） |
| 当研究機関におけるＣＯＩ委員会設置の有無 | 有 ■　無 □（無の場合は委託先機関：　） |
| 当研究に係るＣＯＩについての報告・審査の有無 | 有 ■　無 □（無の場合はその理由：　） |
| 当研究に係るＣＯＩについての指導・管理の有無 | 有 □　無 ■（有の場合はその内容：　） |

（留意事項）　・該当する□にチェックを入れること。

・分担研究者の所属する機関の長も作成すること。

平成31年　4月　16日

国立保健医療科学院長　殿

機関名　国立大学法人広島大学

所属研究機関長　職　名　学長

氏　名　越智　光夫　　印

次の職員の平成30年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

1．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

2．研究課題名　難治性血管腫・血管奇形・リンパ管腫・リンパ管腫症および関連疾患についての調査研究

3．研究者名　（所属部局・職名）　広島大学　大学院医系科学研究科　疫学・疾病制御学　教授

（氏名・フリガナ）　田中　純子　　タナカ　ジュンコ

4．倫理審査の状況

| | 該当性の有無 | 左記で該当がある場合のみ記入（※1） | | |
|---|---|---|---|---|
| | 有　無 | 審査済み | 審査した機関 | 未審査（※2） |
| ヒトゲノム・遺伝子解析研究に関する倫理指針 | □　■ | □ | | □ |
| 遺伝子治療等臨床研究に関する指針 | □　■ | □ | | □ |
| 人を対象とする医学系研究に関する倫理指針（※3） | □　■ | □ | | □ |
| 厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針 | □　■ | □ | | □ |
| その他、該当する倫理指針があれば記入すること（指針の名称：　　） | □　■ | □ | | □ |

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

5．厚生労働分野の研究活動における不正行為への対応について

| | |
|---|---|
| 研究倫理教育の受講状況 | 受講 ■　未受講 □ |

6．利益相反の管理

| | |
|---|---|
| 当研究機関におけるＣＯＩの管理に関する規定の策定 | 有 ■　無 □（無の場合はその理由：　　） |
| 当研究機関におけるＣＯＩ委員会設置の有無 | 有 ■　無 □（無の場合は委託先機関：　　） |
| 当研究に係るＣＯＩについての報告・審査の有無 | 有 ■　無 □（無の場合はその理由：　　） |
| 当研究に係るＣＯＩについての指導・管理の有無 | 有 □　無 ■（有の場合はその内容：　　） |

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

平成 31 年 2 月 4 日

国立保健医療科学院長　殿

機関名　国立大学法人岐阜大学

所属研究機関長　職　名　医学部附属病院長

氏　名　吉　田　和　弘　印

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　難治性血管腫・血管奇形・リンパ管腫・リンパ管腫症および関連疾患についての調査研究

３．研究者名　（所属部局・職名）　医学部附属病院　・　講師

（氏名・フリガナ）　小関　道夫　・　オゼキ　ミチオ

４．倫理審査の状況

| | 該当性の有無 | 左記で該当がある場合のみ記入（※1） | | |
|---|---|---|---|---|
| | 有　無 | 審査済み | 審査した機関 | 未審査（※2） |
| ヒトゲノム・遺伝子解析研究に関する倫理指針 | □　■ | □ | | □ |
| 遺伝子治療等臨床研究に関する指針 | □　■ | □ | | □ |
| 人を対象とする医学系研究に関する倫理指針（※3） | ■　□ | ■ | 岐阜大学大学院医学系研究科医学研究等倫理審査委員会 | □ |
| 厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針 | □　■ | □ | | □ |
| その他、該当する倫理指針があれば記入すること（指針の名称：　　） | □　■ | □ | | □ |

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

| | |
|---|---|
| 研究倫理教育の受講状況 | 受講 ■　未受講 □ |

６．利益相反の管理

| | |
|---|---|
| 当研究機関におけるＣＯＩの管理に関する規定の策定 | 有 ■　無 □（無の場合はその理由：　　） |
| 当研究機関におけるＣＯＩ委員会設置の有無 | 有 ■　無 □（無の場合は委託先機関：　　） |
| 当研究に係るＣＯＩについての報告・審査の有無 | 有 ■　無 □（無の場合はその理由：　　） |
| 当研究に係るＣＯＩについての指導・管理の有無 | 有 □　無 ■（有の場合はその内容：　　） |

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

平成31年　3月　27日

国立保健医療科学院長　殿

機関名　学校法人 自治医科大学

所属研究機関長　職　名　学長

氏　名　永井良三　印

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　難治性血管腫・血管奇形・リンパ管腫・リンパ管腫症および関連疾患についての調査研究

３．研究者名　（所属部局・職名）　学校法人自治医科大学・とちぎ子ども医療センター小児科・教授

（氏名・フリガナ）　森本　哲　・　モリモト　アキラ

４．倫理審査の状況

| | 該当性の有無 | 左記で該当がある場合のみ記入（※1） | | |
|---|---|---|---|---|
| | 有　無 | 審査済み | 審査した機関 | 未審査（※2） |
| ヒトゲノム・遺伝子解析研究に関する倫理指針 | □　☑ | □ | | □ |
| 遺伝子治療等臨床研究に関する指針 | □　☑ | □ | | □ |
| 人を対象とする医学系研究に関する倫理指針（※3） | □　☑ | □ | | □ |
| 厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針 | □　☑ | □ | | □ |
| その他、該当する倫理指針があれば記入すること（指針の名称：　） | □　☑ | □ | | □ |

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

| | |
|---|---|
| 研究倫理教育の受講状況 | 受講 ☑　未受講 □ |

６．利益相反の管理

| | |
|---|---|
| 当研究機関におけるＣＯＩの管理に関する規定の策定 | 有 ☑　無 □（無の場合はその理由：　） |
| 当研究機関におけるＣＯＩ委員会設置の有無 | 有 ☑　無 □（無の場合は委託先機関：　） |
| 当研究に係るＣＯＩについての報告・審査の有無 | 有 ☑　無 □（無の場合はその理由：　） |
| 当研究に係るＣＯＩについての指導・管理の有無 | 有 □　無 ☑（有の場合はその内容：　） |

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

平成31年　3月　15日

国立保健医療科学院長　殿

機関名　国立研究開発法人
国立成育医療研究センター

所属研究機関長　職　名　理事長

氏　名　五十嵐　隆　　印

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　難治性血管腫・血管奇形・リンパ管腫・リンパ管腫症および関連疾患についての調査研究

３．研究者名　（所属部局・職名）　臨床研究センター 生命倫理研究室　・　室長

（氏名・フリガナ）　掛江　直子　・　カケエ　ナオコ

４．倫理審査の状況

| | 該当性の有無 | 左記で該当がある場合のみ記入（※1） | | |
|---|---|---|---|---|
| | 有　無 | 審査済み | 審査した機関 | 未審査（※2） |
| ヒトゲノム・遺伝子解析研究に関する倫理指針 | □　■ | □ | | □ |
| 遺伝子治療等臨床研究に関する指針 | □　■ | □ | | □ |
| 人を対象とする医学系研究に関する倫理指針（※3） | □　■ | □ | | □ |
| 厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針 | □　■ | □ | | □ |
| その他、該当する倫理指針があれば記入すること（指針の名称：　） | □　■ | □ | | □ |

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

| | |
|---|---|
| 研究倫理教育の受講状況 | 受講 ■　未受講 □ |

６．利益相反の管理

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|---|---|
| 当研究機関におけるＣＯＩの管理に関する規定の策定 | 有 ■　無 □（無の場合はその理由：　） |
| 当研究機関におけるＣＯＩ委員会設置の有無 | 有 ■　無 □（無の場合は委託先機関：　） |
| 当研究に係るＣＯＩについての報告・審査の有無 | 有 ■　無 □（無の場合はその理由：　） |
| 当研究に係るＣＯＩについての指導・管理の有無 | 有 □　無 ■（有の場合はその内容：　） |

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

2019年　3月　11日

国立保健医療科学院長　殿

機関名　埼玉県立小児医療センター

所属研究機関長　職　名　病院長

氏　名　小川潔　　印

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　難治性血管腫・血管奇形・リンパ管腫・リンパ管腫症および関連疾患についての調査研究

３．研究者名　（所属部局・職名）　血液腫瘍科・科長兼部長

（氏名・フリガナ）　康勝好・コウカツヨシ

４．倫理審査の状況

| | 該当性の有無 | 左記で該当がある場合のみ記入（※1） | | |
|---|---|---|---|---|
| | 有　無 | 審査済み | 審査した機関 | 未審査（※2） |
| ヒトゲノム・遺伝子解析研究に関する倫理指針 | □　■ | □ | | □ |
| 遺伝子治療等臨床研究に関する指針 | □　■ | □ | | □ |
| 人を対象とする医学系研究に関する倫理指針（※3） | □　■ | □ | | □ |
| 厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針 | □　■ | □ | | □ |
| その他、該当する倫理指針があれば記入すること（指針の名称：　　） | □　■ | □ | | □ |

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

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|---|---|
| 研究倫理教育の受講状況 | 受講 ■　未受講 □ |

６．利益相反の管理

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|---|---|
| 当研究機関におけるＣＯＩの管理に関する規定の策定 | 有 ■　無 □（無の場合はその理由：　　） |
| 当研究機関におけるＣＯＩ委員会設置の有無 | 有 ■　無 □（無の場合は委託先機関：　　） |
| 当研究に係るＣＯＩについての報告・審査の有無 | 有 ■　無 □（無の場合はその理由：　　） |
| 当研究に係るＣＯＩについての指導・管理の有無 | 有 □　無 ■（有の場合はその内容：　　） |

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

平成　31年　3月　8日

国立保健医療科学院長　殿

機関名　国立大学法人新潟大学

所属研究機関長　職　名　学長

氏　名　髙橋　姿　印

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　難治性血管腫・血管奇形・リンパ管腫・リンパ管腫症および関連疾患についての調査研究

３．研究者名　（所属部局・職名）　医歯学総合研究科・准教授

（氏名・フリガナ）　木下　義晶・キノシタ　ヨシアキ

４．倫理審査の状況

| | 該当性の有無 | 左記で該当がある場合のみ記入（※1） | | |
|---|---|---|---|---|
| | 有　無 | 審査済み | 審査した機関 | 未審査（※2） |
| ヒトゲノム・遺伝子解析研究に関する倫理指針 | □　■ | □ | | □ |
| 遺伝子治療等臨床研究に関する指針 | □　■ | □ | | □ |
| 人を対象とする医学系研究に関する倫理指針（※3） | □　■ | □ | | □ |
| 厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針 | □　■ | □ | | □ |
| その他、該当する倫理指針があれば記入すること（指針の名称：　） | □　■ | □ | | □ |

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

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|---|---|
| 研究倫理教育の受講状況 | 受講 ■　未受講 □ |

６．利益相反の管理

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| 当研究機関におけるＣＯＩの管理に関する規定の策定 | 有 ■　無 □（無の場合はその理由：　） |
| 当研究機関におけるＣＯＩ委員会設置の有無 | 有 ■　無 □（無の場合は委託先機関：　） |
| 当研究に係るＣＯＩについての報告・審査の有無 | 有 ■　無 □（無の場合はその理由：　） |
| 当研究に係るＣＯＩについての指導・管理の有無 | 有 □　無 ■（有の場合はその内容：　） |

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

平成　31　年　3月　29日

国立保健医療科学院長　殿

機関名　和歌山県立医科大学

所属研究機関長　職　名　　学長

氏　名　　宮下和久　　印

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　難治性血管腫・血管奇形・リンパ管腫・リンパ管腫症および関連疾患についての調査研究

３．研究者名　（所属部局・職名）　医学部・教授

（氏名・フリガナ）　神人正寿・ジンニンマサトシ

４．倫理審査の状況

| | 該当性の有無 | 左記で該当がある場合のみ記入（※1） | | |
|---|---|---|---|---|
| | 有　無 | 審査済み | 審査した機関 | 未審査（※2） |
| ヒトゲノム・遺伝子解析研究に関する倫理指針 | □　■ | □ | | □ |
| 遺伝子治療等臨床研究に関する指針 | □　■ | □ | | □ |
| 人を対象とする医学系研究に関する倫理指針（※3） | □　■ | □ | | □ |
| 厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針 | □　■ | □ | | □ |
| その他、該当する倫理指針があれば記入すること（指針の名称：　　） | □　■ | □ | | □ |

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

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|---|---|
| 研究倫理教育の受講状況 | 受講 ■　未受講 □ |

６．利益相反の管理

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|---|---|
| 当研究機関におけるＣＯＩの管理に関する規定の策定 | 有 ■　無 □（無の場合はその理由：　　） |
| 当研究機関におけるＣＯＩ委員会設置の有無 | 有 ■　無 □（無の場合は委託先機関：　　） |
| 当研究に係るＣＯＩについての報告・審査の有無 | 有 ■　無 □（無の場合はその理由：　　） |
| 当研究に係るＣＯＩについての指導・管理の有無 | 有 □　無 ■（有の場合はその内容：　　） |

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

平成３１年　３月１１日

国立保健医療科学院長　殿

機関名　国立研究開発法人国立成育医療研究センター

所属研究機関長　職　名　理事長

氏　名　五十嵐　隆　　印

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　難治性血管腫・血管奇形・リンパ管腫・リンパ管腫症および関連疾患についての調査研究

３．研究者名　（所属部局・職名）　臓器・運動器病態外科部外科　診療部長

（氏名・フリガナ）　藤野　明浩　フジノ　アキヒロ

４．倫理審査の状況

| | 該当性の有無 | | 左記で該当がある場合のみ記入（※1） | | |
|---|---|---|---|---|---|
| | 有 | 無 | 審査済み | 審査した機関 | 未審査（※2） |
| ヒトゲノム・遺伝子解析研究に関する倫理指針 | □ | ■ | □ | | □ |
| 遺伝子治療等臨床研究に関する指針 | □ | ■ | □ | | □ |
| 人を対象とする医学系研究に関する倫理指針（※3） | ■ | □ | ■ | 国立成育医療研究センター<br>慶応義塾大学 | □ |
| 厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針 | □ | ■ | □ | | □ |
| その他、該当する倫理指針があれば記入すること<br>（指針の名称：　　） | □ | ■ | □ | | □ |

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

| | |
|---|---|
| 研究倫理教育の受講状況 | 受講 ■　未受講 □ |

６．利益相反の管理

| | |
|---|---|
| 当研究機関におけるＣＯＩの管理に関する規定の策定 | 有 ■　無 □（無の場合はその理由：　　） |
| 当研究機関におけるＣＯＩ委員会設置の有無 | 有 ■　無 □（無の場合は委託先機関：　　） |
| 当研究に係るＣＯＩについての報告・審査の有無 | 有 ■　無 □（無の場合はその理由：　　） |
| 当研究に係るＣＯＩについての指導・管理の有無 | 有 □　無 ■（有の場合はその内容：　　） |

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

31年4月15日

国立保健医療科学院長　殿

機関名　国立大学法人 信州大学

所属研究機関長　職　名　学長

氏　名　濱田州博　印

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　難治性血管腫・血管奇形・リンパ管腫・リンパ管腫症および関連疾患についての調査研究

３．研究者名　（所属部局・職名）医学部・教授

（氏名・フリガナ）杜 俊弥、ユズリハ シュンヤ

４．倫理審査の状況

| | 該当性の有無 | | 左記で該当がある場合のみ記入（※1） | | |
|---|---|---|---|---|---|
| | 有 | 無 | 審査済み | 審査した機関 | 未審査（※2） |
| ヒトゲノム・遺伝子解析研究に関する倫理指針 | □ | ☑ | □ | | □ |
| 遺伝子治療等臨床研究に関する指針 | □ | ☑ | □ | | □ |
| 人を対象とする医学系研究に関する倫理指針（※3） | □ | ☑ | □ | | □ |
| 厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針 | □ | ☑ | □ | | □ |
| その他、該当する倫理指針があれば記入すること（指針の名称：　） | □ | ☑ | □ | | □ |

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。

（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

| | |
|---|---|
| 研究倫理教育の受講状況 | 受講 ☑　未受講 □ |

６．利益相反の管理

| | |
|---|---|
| 当研究機関におけるＣＯＩの管理に関する規定の策定 | 有 ☑　無 □（無の場合はその理由：　） |
| 当研究機関におけるＣＯＩ委員会設置の有無 | 有 ☑　無 □（無の場合は委託先機関：　） |
| 当研究に係るＣＯＩについての報告・審査の有無 | 有 ☑　無 □（無の場合はその理由：　） |
| 当研究に係るＣＯＩについての指導・管理の有無 | 有 □　無 ☑（有の場合はその内容：　） |

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

平成31年　3月　31日

国立保健医療科学院長　殿

機関名　国立大学法人神戸大学

所属研究機関長　職　名　学長

氏　名　武田　廣　　印

次の職員の平成30年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

1．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

2．研究課題名　難治性血管腫・血管奇形・リンパ管腫・リンパ管腫症および関連疾患についての調査研究

3．研究者名　（所属部局・職名）医学部附属病院・特命講師

（氏名・フリガナ）野村　正・ノムラ　タダシ

4．倫理審査の状況

| | 該当性の有無 | 左記で該当がある場合のみ記入（※1） | | |
|---|---|---|---|---|
| | 有　無 | 審査済み | 審査した機関 | 未審査（※2） |
| ヒトゲノム・遺伝子解析研究に関する倫理指針 | □　☑ | □ | | □ |
| 遺伝子治療等臨床研究に関する指針 | □　☑ | □ | | □ |
| 人を対象とする医学系研究に関する倫理指針（※3） | □　☑ | □ | | □ |
| 厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針 | □　☑ | □ | | □ |
| その他、該当する倫理指針があれば記入すること（指針の名称：　　） | □　☑ | □ | | □ |

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

なし

（※2）未審査に場合は、その理由を記載すること。

（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

5．厚生労働分野の研究活動における不正行為への対応について

| | |
|---|---|
| 研究倫理教育の受講状況 | 受講 ☑　未受講 □ |

6．利益相反の管理

| | |
|---|---|
| 当研究機関におけるＣＯＩの管理に関する規定の策定 | 有 ☑　無 □（無の場合はその理由：　　） |
| 当研究機関におけるＣＯＩ委員会設置の有無 | 有 ☑　無 □（無の場合は委託先機関：　　） |
| 当研究に係るＣＯＩについての報告・審査の有無 | 有 ☑　無 □（無の場合はその理由：　　） |
| 当研究に係るＣＯＩについての指導・管理の有無 | 有 □　無 ☑（有の場合はその内容：　　） |

（留意事項）　・該当する□にチェックを入れること。

・分担研究者の所属する機関の長も作成すること。

2019年　3月　29日

国立保健医療科学院長　殿

機関名　学校法人聖路加国際大学

所属研究機関長　職　名　学　長

氏　名　福井　次矢

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　難治性血管腫・血管奇形・リンパ管腫・リンパ管腫症および関連疾患についての調査研究

３．研究者名　（所属部局・職名）聖路加国際病院　放射線科・医幹

（氏名・フリガナ）野崎　太希　・　ノザキ　タイキ

４．倫理審査の状況

| | 該当性の有無 | 左記で該当がある場合のみ記入（※1） | | |
|---|---|---|---|---|
| | 有　無 | 審査済み | 審査した機関 | 未審査（※2） |
| ヒトゲノム・遺伝子解析研究に関する倫理指針 | □　■ | □ | | □ |
| 遺伝子治療等臨床研究に関する指針 | □　■ | □ | | □ |
| 人を対象とする医学系研究に関する倫理指針（※3） | □　■ | □ | | □ |
| 厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針 | □　■ | □ | | □ |
| その他、該当する倫理指針があれば記入すること（指針の名称：　） | □　■ | □ | | □ |

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

| | |
|---|---|
| 研究倫理教育の受講状況 | 受講 ■　未受講 □ |

６．利益相反の管理

| | |
|---|---|
| 当研究機関におけるＣＯＩの管理に関する規定の策定 | 有 ■　無 □（無の場合はその理由：　） |
| 当研究機関におけるＣＯＩ委員会設置の有無 | 有 ■　無 □（無の場合は委託先機関：　） |
| 当研究に係るＣＯＩについての報告・審査の有無 | 有 ■　無 □（無の場合はその理由：　） |
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（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。