表 23 つづき

Study	# subjects/ # PAVMs	diagnosis of HHT	mean age (years) (range)	intervention done	% with follow-up	mean follow-up (months)
Lee et al. 1997[18]	45/52 (Large PAVMs)	87%	42 (12～73)	100%	100%	56
Chilvers et al. 1990[31]	15/—	73%	41 (13～63)	100%	100%	3
White et al. 1988[17]	76/276	88%	36 (5～76)	100%	95%	minimum 3
Gershon et al. 2001[19]	7/13 pregnancy	100%	28 (24～34)	100%	100%	30
Faughnan et al. 2004[35]	42/172 pediatric	86%	12 (4～18)	100%	90%	84

brach plex＝brachial plexus
complix＝complication
embo＝embolization
paradox＝paradoxical
pulm HTN＝pulmonary hypertension
DVT＝deep vein thrombosis
Tc99 MAA＝shunt measurement using Technetium 99 labeled albumin macroaggregates
TIA＝transient ischaemic attack

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post-embolization outcome	frequency post-embo outcome	procedural complication	frerquency complication
reperfusion	15%	pleurisy air embo paradox embo	31% 2% 4%
improved SpO_2 pre-post improved shunt ($100\%O_2$) pre-post improved peak work capacity pre-post	$p<0.05$ $p<0.001$ 60%	DVT pulm infarct	8% 8%
tech success improved O_2 pre-post TIA	100% 77% 2%	pleurisy air embo paradox embo DVT	10% 5% 3% 1%
tech success estimated fetal radiation dose	100% 50~220 mRad	pleurisy fetal/childhood complications	29% 0%
improved PaO_2 pre-post absence of PAVM complex (FOCAL group) absence of PAVM complex (DIFFUSE group) reperfusion	$p<0.003$ 100% 83% (2 deaths, 1 from brain abscess, 1 from lung transplant) 15%	long-term pleurisy other pain angina paradox embo device misplaced brach plex injury	0% 24% 2% 1% 0% 3% 1%

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〈佐藤一洋〉

5 肝動静脈奇形

POINTS

◉無症状の肝病変は治療不要であり，経過観察のみでよい．
◉症状のある患者では，内科療法，肝動脈塞栓術，肝移植などが考慮される．
◉肝動脈塞栓術は再発率が高く，死亡など重篤な合併症の可能性がある．
◉現在，肝疾患を伴うHHT患者において唯一根治可能な治療法は，肝移植である．

1．肝動静脈奇形の背景

肝動静脈奇形は，HHT患者の32～78%に合併するが，肝動静脈奇形に関連する症状は約8%の患者にしか出現しないと報告されている[1]．肝動静脈奇形の合併症としては，高拍出性心不全，門脈圧亢進症，胆管壊死などがあげられる[1,2]．

肝動静脈奇形の診断に関しては，超音波ドプラーエコー法，MRI，CTなど非侵襲的検査法の有用性が報告されている．血管撮影では，末梢血管拡張症，肝動脈拡張，シャント（肝動脈-門脈，肝動脈-肝静脈，門脈-肝静脈）などの異常所見がみられる[1,2]．HHT患者のスクリーニングによる肝病変の有病率は，超音波ドプラーエコー法で32～72%，3次元CTで67～78%と報告がされている（表30）[1,3-7]．

生検による組織学的診断は，典型的な画像所見がある場合には，肝動静脈奇形破裂などのリスクから不必要である[1]．結節性過形成 nodular hyperplasia の頻度が高いが[8]，しかし，これらの所見は生検なしでも画像所見から診断が可能である[1]．

2．肝動静脈奇形の治療

一般的に無症状の肝病変は治療不要であり，経過観察のみでよく，症状のある患者では，内科的治療，肝動脈塞栓術，肝移植が考慮される[1,2]．肝動脈塞栓術，肝移植に関しては，3つの研究成績が報告されている（表31）[1,9-11]．

a．内科的治療

高拍出性心不全では，通常，輸血による貧血の改善，薬剤による不整脈の改善などの内科的治療が行われる．妊婦の患者では，出産は急ぐべきで分娩後に心不全は軽快することが多い[2]．門脈圧亢進症に関しては肝硬変患者と同様に治療されるべきであり，第1選択は，塩分の制限，フロセミドやスピロノラクトンなどの利尿薬，不反応性腹水では治療的除水後にプラズマ投与が考慮される[2,12,13]．ある程度大きな食道静脈瘤に対しては，予防的にβブロッカー投与か，βブロッカーの投与ができない患者では内視鏡による静脈瘤結紮術が施行される[2]．食道あるいは胃静脈瘤からの出血に対しては，輸液あるいは輸血が行われる．胃食道内視鏡は，出血後12時間以内に施行し，診断後に結紮術あるいは硬化療法が行われる．胆汁うっ帯を伴う胆管炎には抗菌薬の全身投与と鎮静剤投与が行われるが，こうした患者では，内視鏡による逆行性胆管造影などの侵襲的検査は上行性胆管炎を惹起するので行うべきでない[2]．

近年，血管内皮増殖因子 vascular endothelial growth factor（VEGF）に対するベバシズマムを用いた抗体療法の有用性が報告されている[14,15]．さらに，サリドマイドが血小板増殖因子 platelet-derived growth factor（PDGF）を介して血管を成熟させHHT患者の鼻出血を軽減させる報告[16]がみられる．これらの報告は，いずれもHHTの分子病態生理に基づく研究であり，将来的に大いに期待できるが，その実際的な応用に関しては，今後の大規模臨床研究による成績が待たれる．

表 30 遺伝性出血性末梢血管拡張症（HHT）における肝動静脈奇形の頻度[1)]

study	n	population	%HHT	type of study	test	findings for liver VMs	frequency of abnormality in liver VMs	prevalence liver VMs detected	gold standard
Memeo et al. 2005[3)]	105	HHT, consecutive patients	100%	screening descriptive	CT	telangiectasia CVMs AV shunt AP shunt AV & AP shunt perfusion abN PHT	50/78 (64%) 20/78 (26%) 40/78 (51%) 16/78 (21%) 22/78 (28%) 46/78 (59%) 46/78 (59%)	78/100 (78%)	no
Ravard et al. 2004[4)]	24 24	HHT, consecutive patients controls	100%	screening descriptive comparative	CT	dilated HA telangiectasia AV shunt AP shunt	16/16 (100%) 12/16 (75%) 5/16 (31%) 3/16 (19%)	16/24 (67%)	no
Buscarini et al. 2004[5)]	346	HHT, members of HHT families	221 (64%)	screening descriptive	Doppler US	mild moderate severe	11/92 (12%) 70/92 (76%) 11/92 (12%)	92/221 (41%)	no
Buscarini et al. 1997[6)]	73	HHT, one family	40 (55%)	screening descriptive	Doppler US	mild moderate severe	3/13 (23%) 3/13 (23%) 7/13 (46%)	13/40 (32%)	angio12/13
Ocran et al. 2004[7)]	22	HHT consecutive patients	100%	screening descriptive	Doppler US	dilated HA dilated intra HA AV shunts	14/16 (88%) 15/16 (94%) 16/16 (100%)	16/22 (73%)	no

abN＝abnormal; AV＝arteriovenous; CVM＝confluent vascular malformations; HA＝hepatic artery; PHT＝portal hypertension; PV＝porto-venous, VM＝vascular malformations;
*4 of 6 in whom the initial diagnosis of HHT was "probable" became definite with the finding of liver VMs
clinical liver VMs＝patients with clinical signs or symptoms of liver VMs

b．肝動脈塞栓術

古くはシャント減少術として肝動脈結紮術が行われた時代もあったが，効果が不確実なこと，あるいは術後死亡を含めた成績がきわめて悪かったために現在では行われない[1,2)]．一方，肝動脈塞栓術は，肝動脈-肝静脈あるいは肝動脈-門脈のシャントを肝動脈の分枝を塞栓することにより減少させることを目的として行われるものである．塞栓術は高拍出性心不全や腸間膜のスティールに関する症状を改善するのには役立つが，しかし，その効果は一過性であり症状は通常再発する[1,2)]．さらに重要なことは，虚血性胆管炎，虚血性胆嚢炎，肝壊死などの虚血性合併症が，門脈圧亢進症例の 50%を含む治療例中の約 30～40%に出現し，結果として肝移植になるかあるいは死亡している[1,9,17)]．肝動脈塞栓術例の 2 年生存率は約 73%である．専門家パネルは，塞栓術後の虚血性障害のリスクは，肝血管障害による胆汁うっ帯のみられる HHT 患者で多くみられるとしている[1,2)]．

c．肝移植

内科的治療にもかかわらず悪化する肝疾患を伴う HHT 患者において，現在のところ，唯一根治可能な治療法は肝移植である[1,2)]．肝移植により大多数の患者で症状は軽減するが，肝移植においては大量の輸血を必要とし，長期の入院を余儀なくされ，術後合併症の頻度も比較的高い[1,2)]．しかしながら，大規模研究[11)]によると肝移植後の 5 年生存率は約 83%であり，全肝臓移植の生存率よりも高いと報告されている．

表31 遺伝性出血性末梢血管拡張症（HHT）における肝動静脈奇形の治療成績[1)]

study	n	clinical types	treatment	median follow-up (months)	outcomes of treatment	frequency of outcomes	complications	frequency of complications
Lerut et al. 2006[11)]	40	14 HF 12 BIL 5 PHT 6 HF+BIL 2 HF+PHT 1 HF+PHT+BIL	trans	58	5-year survival HF improved HF stable HF alone death BIL+/−HF death PHT+/−HF death	83% 18/24 (75%) 5/24 (21%) 1/24 (4%) 4/18 (22%) 3/8 (38%)	intraoper bleed* GI bleed* CHF* acute rejection* chronic rejection* graft failure* cerebral bleed* PAVM bleed* non-fatal complications	1/40 (3%) 1/40 (3%) 1/40 (3%) 1/40 (3%) 1/40 (3%) 1/40 (3%) 1/40 (3%) 1/40 (3%) 24/40 (60%)
Chavan et al. 2004[9)]	15	11 HF 5 Steal 4 PHT	staged HA embo	28	Alive HF alive HF improved Steal alive Steal improved PHT alive PHT improved	11/15 (73%) 10/11 (91%) 10/11 (91%) 5/5 (100%) 5/5 (100%) 2/4 (50%) 2/4 (50%)	hepatic necrosis* cholangits/ cholecystitis*	1/15 (7%) 3/15 (20%)
Azoulay et al. 2002[10)]	6	3 BIL 2 PHT 1 HF+BIL	transplant	57	Alive BIL alive PHT alive HF+BIL alive	4/6 (67%) 3/3 (100%) 1/2 (50%) 0/1 (0%)	GI bleeding* peritonitis*	1/6 (17%) 1/6 (17%)

HA=hepatic artery, HF=high output heart failure; PHT=portal hypertension; BIL=biliary
*Causing death

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3 妊娠の影響

POINTS

◉HHT 合併妊娠では PAVM の増大，胎児の低酸素血症による子宮内発育遅延の可能性が示されている．
◉妊娠後期での喀血，血胸も報告されている．
◉通常分娩に比較すると HHT 合併妊娠は高リスクである．
◉妊娠，出産する可能性のある患者は，妊娠前の診断と治療が原則である．
◉妊娠前の肺動静脈奇形のスクリーニングとインターベンション治療が有効である．

1．HHT 合併妊娠の問題点

a．問題となる合併症

HHT の頻度は欧米では 5,000～8,000 人に 1 人であり[1]，女性に多く 10,000 人に対し 2 人である[2]．本邦では欧米に比しまれな疾患と認識されていたが，本邦における頻度も欧米と変わらないとの報告がある[3,4]．したがって，HHT 合併妊娠を経験する頻度も欧米なみになることが予想される．無症状の HHT 女性をスクリーニングすると，肺動静脈奇形（PAVM）が 48%[5]，脳 AVM（CAVM）が 10%[6]，肝 AVM がおよそ 30%[7]，背髄 AVM（spinal AVM）が 0.3～1%にみられた．

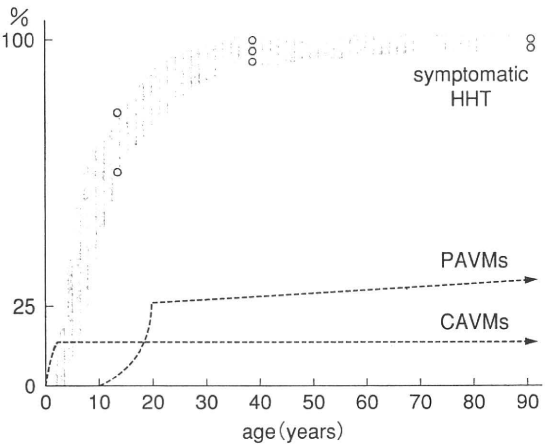

図 130 HHT 症状の出現年齢（Begbie ME, et al. Postgrad Med J. 2003; 79: 18-24）[10]
PAVM: pulmonary AVM, CAVM: cerebral AVM

b．肺動静脈奇形（PAVM）

HHT 患者の妊娠の際に，特に問題となるのは PAVM の合併である．AVM は生下時より存在しているが，通常幼少期には無症状で，20～30 歳代で臨床的に発見されることが多い[8,9]（図 130）[10]．PAVM の合併症としては，右-左シャントによる低酸素血症，瘤の破裂による喀血・血胸，中枢神経系の塞栓症，膿瘍などがある[11-15]．また，妊娠中の PAVM の増大も報告されている[12-14,16-18]．増大は妊娠第 2～3 期（4～5 カ月）に多くみられ，それに伴い合併症の生じる危険性も高くなる[14,16,19-21]．妊娠中の PAVM の増大，瘤の破裂の機序は，妊娠中は体循環量が 40%，心拍出量が 30～50%増加するのに加えて[20,22]，プロゲステロンの上昇により小動脈平滑筋が弛緩し PAVM 内の血管の拡張をきたし，PAVM へ血流の増加をきたすため PAVM が増大，破裂する危険が高まると考えられている[20,23]．

HHT 患者 47 名の妊娠 161 回のうち，PAVM を認めない 138 回と PAVM を認める 23 回を比較した結果，PAVM のない妊娠では 1 例の脳血管の合併症を認めたのみであったのに対し，PAVM のある妊娠では 6 例の肺内シャントの悪化，2 例の致死的な肺出血，2 例の脳血管の合併症が認められた[16]．また，PAVM を伴う妊娠 26 症例のレビューでは，50%に血胸，26%に血痰，15%にシャント増悪，8%に脳梗塞を認め，うち 3 例が死亡（肺出血 2 例，脳梗塞 1 例）した．これらの症状発現時期は，妊娠 2～3 期が 85%であった[20]．

c. 脳動静脈奇形(CAVM), 脊髄動静脈奇形(spinal AVM)

PAVM に次いで考慮を要するのは中枢神経系に生じた動静脈奇形である. HHT に脳動静脈奇形を合併した場合でも, 多くは正常な妊娠経過をとるが, 分娩に際しては, 脳出血予防のために選択的帝王切開術が望ましい. その場合, HHT 患者の 1〜2%に合併する脊髄動静脈奇形(spinal AVM)は硬膜外麻酔を行う場合に危険であり, 妊娠前に MRI 検査でその存在を否定する必要がある[10].

d. 胎児への影響

HHT が胎児に与える影響について考慮する必要がある. HHT 合併妊娠でも流産率は増加しないとされているが, びまん性に PAVM が認められる症例で低酸素症を伴うものでは流産率が上昇し, 低酸素症を是正すると妊娠に至り健児を獲得したとする報告もみられる[24]. また, PAVM を伴う HHT のため妊娠中に慢性的な低酸素が持続すれば子宮内胎児発育遅延の原因となりうる[24,25].

e. 患者教育

患者への説明も重要である. ほとんどの患者夫婦にとって出産は平穏無事なものであるが, HHT は常染色体優性遺伝形式をとるため, 胎児には 50%の確率で遺伝する. また前述の PAVM の増大による合併症が起こりうること[2,10]など, 遺伝性疾患としての患者教育を行う必要がある.

2. 治　療

a. 妊娠前の治療

PAVM の治療が適応となるのは, 右-左シャントからの奇異性塞栓症による一過性脳虚血発作(TIA)や脳梗塞, また右-左シャントを介し静脈系から動脈系に細菌が移行して起こる脳膿瘍の危険性が増大する状況である. 具体的には, PAVM が進行性に増大する場合, 塞栓症を併発する場合, 症候性の低酸素血症を伴う場合, そして PAVM の径が 2 cm 以上または流入動脈が 3 mm 以上の場合とされる[26,27]. PAVM の治療は, 低侵襲性, 低合併症率, 繰り返し可能な点, 機材の進歩などから, 手術より塞栓術が第 1 選択となっている[28,29].

妊娠 HHT 女性の場合には前述のような合併症を伴うことがあるため, HHT 女性に対しては, 妊娠前に PAVM の有無および程度について精査を行うべきである[19]. 143 名の HHT および PAVM 患者のうち, 11 例(8%)に入院を必要とする喀血, 血胸がみられた. 11 例中 7 例が女性で, 3 人が妊娠中に肺出血があった. その 11 家族をスクリーニングしたところ 45 人中 36 人(80%)に肺血管造影で PAVM がみられた. この結果から HHT 患者の家族で, 特に出産可能な年代の女性はスクリーニングが推奨される[19]. さらに HHT 女性 199 名 484 妊娠での合併症の検討では, 74%が妊娠前に HHT と診断されておらず, 1.4%が PAVM 出血, 1.2%が脳卒中, 1.0%に母体死亡であった. 通常分娩に比較すると HHT 合併妊娠は高リスクと考えられるが, 妊娠前に HHT の診断を得て, インターベンションされている群の予後が良好であったこと[2]より, 妊娠前に PAVM を治療することが推奨される[2,10,25].

b. 妊娠中の治療

妊娠中に施行したカテーテル塞栓術の報告によれば, 7 例の妊娠中の女性に PAVM の経カテーテル的塞栓術が施行され, 全例で明らかな合併症を生じることなく, 無事出産に至っている. 塞栓術は妊娠 16〜36 週の間に施行されており, 胎児被曝は 50〜220mrad であった[20]. 本邦においても, 未治療であった HHT 合併妊娠に対して, 妊娠第 9 週に被曝の線量当量が頸部で 1.243 mSv, 腹部で 0.129 mSv と安全にコイル塞栓を施行しえた報告がある[30].

妊娠中の経カテーテル塞栓術においては, 胎児被曝の問題が重要である. 放射線の影響には 2 種類あり,

表 36 職業被曝に対する線量限度(館　悦子, 他. 日胸. 2002; 61: 542-6)[30]

実行線量限度	100 mSv/5 年
	50 mSv/1 年
女子	5 mSv/3 カ月
妊娠から出産までの内部被曝	1 mSv
等価線量	
眼の水晶体	150 mSv/年
皮膚	500 mSv/年
手および足	500 mSv/年
妊婦の腹部表面	2 mSv(妊娠期間中)

表37　胎児期の放射線被曝による影響（館　悦子，他．日胸．2002；61：542-6）[30]

	影響	胎児期の分類（受精後）	閾線量
確定的影響	胚死亡	着床前期（0～9日）	50～100 mSv
	奇形	器官形成期（2～8週）	100 mSv
	発育遅滞	胎児期（8週～出生）	100 mSv
	精神発達遅滞	胎児期（8週～出生　特に8～15週）	120～200 mSv
確率的影響	発癌	全期間	なし
	遺伝的影響	全期間	

影響の発生する最小の線量である閾（しきい）線量を超えた場合に影響があらわれる確定的影響と，閾線量がなく，被曝線量に比例して影響の発生率が増加すると考えられる確率的影響とに分けられる．胎児期の放射線による影響は，被曝の時期とその閾線量について国際放射線防護委員会（International Commission on Radiation Protection：ICRP）から勧告（表36，37）[30-32]が出されている．熟練した術者によって通常の塞栓術が施行されれば，この閾線量を超えることはまずないと考えられる．塞栓術を施行する時期に関しては，母体の合併症の防止という観点からすれば，妊娠第2期以降（14週以降）ではPAVM増大による合併症が増加することから，それ以前の施行が望ましい．一方，胎児への放射線の影響からは，できるだけ遅い時期のほうが安全である．特に，器官形成期までは発生学的にも奇形発生の感受性の強い時期であり，できるだけ避けたほうがよい．

3．HHT合併妊娠への対応

通常分娩に比較するとHHT合併妊娠は高リスクであり，妊娠前に肺動静脈奇形のスクリーニングと治療が必要である．妊娠を考えているHHTの女性患者は特に肺動静脈奇形の検査を受けるべきであり，経カテーテル塞栓術により，肺からの塞栓症や低酸素血症を予防・減少させ，妊娠合併症を軽減させることができる．また突然の血痰，呼吸困難があれば，ただちに受診し，緊急入院する必要がある[2,10]．妊娠，出産する可能性のある患者は，妊娠前の治療が原則であるが，未治療のPAVMの妊娠例では，妊娠初期には，酸素吸入により胎児の低酸素血症を予防し，待機的に妊娠中でも塞栓術を試みるという選択肢もある[21,24,30]．

妊娠前のHHT症例をみたときは内科，皮膚科，耳鼻科などの専門医とも連携をとりつつ，詳細な問診，全身検索を行い，十分な疾患説明と遺伝疾患としての患者の教育，妊娠前の治療を行う[2,10]．またHHT合併妊娠の際も，単科のみで対応するのではなく，産科，内科，皮膚科，耳鼻科など医療チームとして出産に向け対応する必要がある[2,10]．

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〈佐野正明〉

4 フォローアップの留意事項

POINTS

- ◉HHT 患者あるいは HHT が疑われる患者は，定期的経過観察を受ける必要がある．
- ◉HHT 患者では深部静脈血栓症の予防が重要である．
- ◉HHT 患者あるいは家族では，脳出血，脳梗塞，脳膿瘍の 3 つのタイプの脳疾患の注意が必要である．
- ◉PAVM 合併 HHT 患者においては，歯科あるいは外科治療の際には，心内膜炎を予防する目的から，予防的な抗生物質の投与が推奨される．
- ◉PAVM 合併 HHT 患者の航空機による旅行では喀血，血胸のリスクがあり，スキューバダイビングは避けるべきである．

1．フォローアップ

確実に HHT と診断された人，家族歴に基づいてリスクがあると判断される人，分子遺伝学的検査による除外ができない人の経過観察には，以下のフォローアップが推奨される[1]．

1）HHT に詳しい医療従事者による年 1 回の鼻出血，その他の出血，息切れ，運動耐容能の低下，頭痛，その他の神経症状の病歴の評価．
2）貧血を適切に治療するための定期的なヘマトクリット/ヘモグロビンの測定．
3）約 3〜5 年毎のコントラスト心臓エコー法あるいは胸部 CT を用いた PAVM の再評価．

2．深部静脈血栓症の予防

HHT 患者では，一般的に重大な虚血性疾患あるいは血栓塞栓症を防ぐ目的で抗凝固療法（あるいは抗血小板療法）が必要になる[2,3]．特に，PAVM に起因する脳膿瘍のために入院治療した HHT 患者では，深部静脈血栓症の危険が高い場合には予防的な抗凝固療法を必要とする[4,5]．もし，深部静脈血栓症が発生したときには，ヘパリンあるいはワルファリンを治療用量で投与する[2]．経験的に，鼻出血は悪化しやすいが，抗凝固療法は多くの患者において十分に耐えることができるが，しかし，消化管出血に関しては十分に注意しなければならない[2,5]．

3．脳卒中のある HHT 患者

HHT 家系の家族が脳卒中様発作を起こした際に，かかりつけ医は，それらには，脳出血，脳梗塞，脳膿瘍の 3 つのタイプがあることを留意する必要があるとともに，HHT の神経学的徴候は，HHT の脳血管奇形による合併症に比べて PAVM を介しての奇異性塞栓症に起因することが多いことも知っておく必要がある[2,6]．

脳膿瘍の補助診断に初期から MRI を考慮するなど，通常の脳卒中の管理指針を変更する必要がある[2,6]．経験的に，虚血性脳血管障害では，抗血小板療法は十分に耐えられる．AVM の存在する可能性がある際の血栓溶解療法は絶対的禁忌であるということは認識される必要がある[7]．

4．歯科治療

PAVM が合併した HHT 患者においては，歯科ある

いは外科治療の際には，心内膜炎を予防する目的から，予防的な抗生物質の投与が推奨されている[8,9]．口腔内細菌と脳膿瘍の関連がエビデンスとして強調されているが，American Heart Association[10]や British NICE ガイドライン[11]では，「感染性心内膜炎のリスクがある器質的な心疾患に対しての予防的抗菌薬投与は，多くの患者では不要である」と，前述の推奨と異なる見解を示している．

5. 航空機による旅行，スキューバダイビング

理論的に，航空機による低酸素血症と静脈血栓症に関する危惧があるが，HHT に関しては限られたデータしか報告されていない．PAVM に起因する低酸素血症にある患者が特に医療相談などなく特に悪化せずに航空機旅行を行った事例がある[2]．一方で，大西洋を横断する旅行直後に脳梗塞や深部静脈血栓症になった症例報告[5]もある．また，飛行中に PAVM の出血（1例は喀血，1例は血胸）の症例報告[12]もみられる．

PAVM のある患者あるいは HHT で右-左シャントが陰性でない患者では，スキューバダイビングは避けるべきである[1]．

6. 展　望

数十年が経過して，近年，HHT の病態・診断・治療に関して，科学的および医学的に大きな進歩がみられる[1,2]．HHT の治療方法や遺伝子診断などに関しては，今後もさらに進歩することが大いに期待されるところである．しかしながら，こうした現況においても，臨床医と科学者にとって最も大切なことは，HHT 患者や家族の声に対して常に十分に耳を傾けることである[2]．

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〈塩谷隆信　村田勝敬〉

Respirology (1998) **4**, 277–280

CASE REPORT

Transcatheter embolization of pulmonary arteriovenous malformations in Rendu–Osler–Weber disease

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Transcatheter embolization of pulmonary arteriovenous malformations in Rendu–Osler–Weber disease
SHIOYA T, KAGAYA M, SANO M, ITO N, WATANABE A, SATO K, ITO T, SASAKI M, HASHIMOTO M, MIURA M. *Respirology* 1998 **3**: 277–280

Abstract Interest in the treatment of the pulmonary arteriovenous malformations (PAVMs) that occur in approximately one-third of patients with Rendu–Osler–Weber (ROW) disease (hereditary haemorrhagic teleangiectasia) has recently been renewed. PAVMs can now be occluded safely by the transvenous placement of detachable balloons or metal coils, thus avoiding the many potential complications of thoracotomy. This study analyses the treatment of eight PAVMs in four ROW patients by transcatheter embolization using detachable balloons or metal coils. After embolization, the mean right-to-left shunt fraction significantly decreased from $39.1 \pm 5.1\%$ to $11.9 \pm 1.1\%$ ($P < 0.05$) and PaO_2 significantly increased from 53.3 ± 7.8 torr to 76.2 ± 8.4 torr ($P < 0.05$). No serious complications occurred. One detachable balloon was deflated, but no recanalization occurred. We conclude that transcatheter embolization is a safe and efficacious treatment for PAVMs associated with ROW disease. Long-term studies are now needed to determine the risk of recanalization in this treatment.

Key words: hereditary haemorrhagic telangiectasia, pulmonary arteriovenous malformations, Rendu–Osler–Weber disease, transcatheter embolization.

INTRODUCTION

Rendu–Osler–Weber (ROW) disease (hereditary haemorrhagic telangiectasia) is an autosomal dominant disease that is characterized by systemic capillary dilation and bleeding diathesis.[1,2] Pulmonary arteriovenous malformations (PAVMs) are rare, mostly congenital, abnormalities of the pulmonary circulation, often associated with ROW disease. They involve direct communications between pulmonary arteries and veins via enlarged, tortuous vascular spaces.[3,4] The right-to-left shunt causes hypoxaemia which may give rise to decreased exercise capacity, dyspnoea and cyanosis. PAVMs can cause two serious complications: haemoptysis or haemothorax from the abnormal vessels, and thrombo-emboli that might result in fatal systemic emboli.[5] Thus, nearly half of all ROW patients with PAVMs report a history of stroke or transient ischaemic attack.[6,7] Brain abscess occurs in 5–14% of ROW patients with PAVM as a result of septic emboli.[8,9]

It is generally accepted that these risks justify the treatment of even asymptomatic PAVMs provided the diameter of the feeding vessels is more than 3 mm.[10] Disadvantages of surgical treatment are loss of the normal lung tissue surrounding the PAVMs and morbidity associated with thoracotomy. Currently, one accepted mode of treatment is the transcatheter embolization of feeding vessels using detachable balloons or metal coils.[11,12] Although some reports concerning embolization of PAVMs have been published, the data on long-term results are limited.[5,13]

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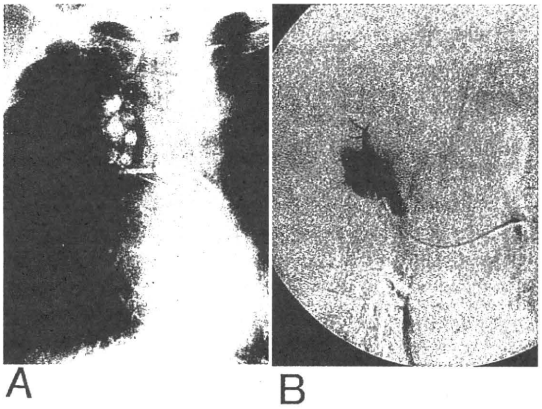

Figure 1 Case 1. (a) Pulmonary angiogram showing large PAVM in the right upper lung. (b) After embolization with two detachable balloons, the pulmonary angiogram shows occlusion of the PAVM and filling of several branches to the normal lung which were not apparent on the original angiogram due to the steel effect of the PAVM.

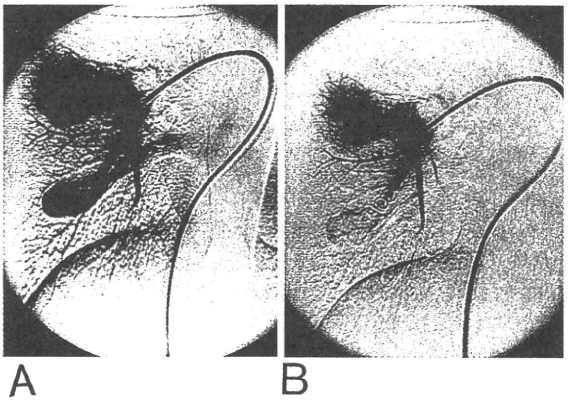

Figure 2 Case 2. (a) Pulmonary angiogram showing PAVM in the right basal lung. (b) Pulmonary angiogram after embolization with a steel coil showing occlusion of PAVM in the right basal lung.

In Japan, only 144 ROW patients and 126 ROW families have been reported to date, with one-third of the ROW patients being complicated by PAVMs.[14, 15] The first choice of treatment is still considered to be surgical resection. To help clarify the treatment of such cases, we therefore present our results of transcatheter embolization of PAVMs associated with ROW disease.

METHODS AND SUBJECTS

Over the last four years, in the Second Department of Internal Medicine at Akita Uiversity School of Medicine, transcatheter embolizations were used to treat four ROW patients with PAVMs. The embolizations were all performed by the same radiologist (M.H.). Following introduction via the femoral vein, pulmonary angiography was performed using a digital subtraction technique. Feeding vessels with a diameter of more than 5 mm were selectively cannulated and embolized with metal coils of

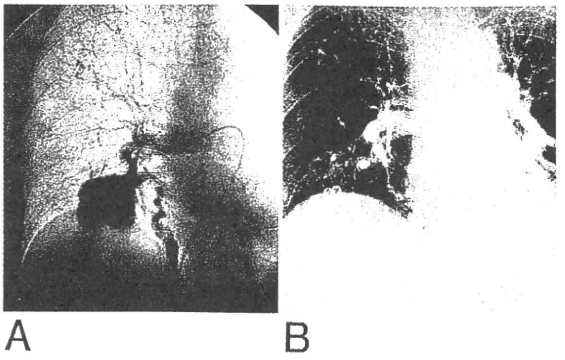

Figure 3 Case 3. (a) Pulmonary angiogram showing two PAVMs in the right basal lung. (b) Pulmonary angiogram after embolization with steel coils showing occlusion of the PAVMs in the right basal lung.

appropriate size (Target Therapeutics, Fremont, California). Additional coils were placed until there was no further flow from the pulmonary circulation. Latex detachable balloons (NYCOMED, Paris, France) with non-polymerizing liquids (radio-opaque agents) were placed using coaxial catheters in one patient (case 1). All PAVMs with accessible feeding vessels larger than 5 mm were embolized. The outcomes were evaluated between the 7th and 14th day after embolization.

The right-to-left shunt fraction was calculated using inhalation of 100% and the following formula:

$$\frac{QS}{QT} = \frac{0.003(P_AO_2 - PaO_2}{0.003(P_AO_2 - PaO_2) + (CaO_2 - CvO_2)}$$

in which P_AO_2 is the ideal alveolar oxygen tension, PaO_2 is the arterial oxygen tension, CaO_2 is the arterial oxygen content, and CvO_2 is the mixed venous oxygen content.

All data are expressed as means $\pm$ the standard errors of the means (SEM), and were analysed using Student's t test (two-tailed) for paired samples. P values of 0.05 or less were considered significant.

RESULTS

Individual results of transcatheter embolization treatment are given in Table 1.* Patients 1 and 2 had a single PAVM and patients 3 and 4 had multiple PAVMs. After embolization, the mean PaO_2 significantly increased from 53.3 ± 7.8 torr to 76.2 ± 8.4 torr ($P < 0.05$), and the mean right–left shunt significantly decreased from $39.1 \pm 5.1\%$ to $11.9 \pm 1.1\%$ ($P < 0.05$). In patient 1, one detachable balloon deflated on the 7th operative day; however, no recanalization occurred.

* Pulmonary angiograms before and after embolization are shown in Figure 1 through Figure 4.

Table 1 Results of embolization in individual patients

Patient age (years) and sex	Number of PAVMs treated	PaO_2 before treatment (torr)	PaO_2 after treatment (torr)	Shunt before treatment (%)	Shunt after treatment (%)
1 43, M	1 (balloon)	64.4	83.6	35.0	13.2
2 19, F	1 (coil)	65.7	86.5	33.1	12.7
3 58, F	2 (coil)	32.1	51.2	NT	NT
4 30, M	4 (coil)	51.1	83.5	49.1	9.8
Mean ± SEM		53.3 ± 7.8	76.2 ± 8.4	39.1 ± 5.1	11.9 ± 1.1

NT, not tested.

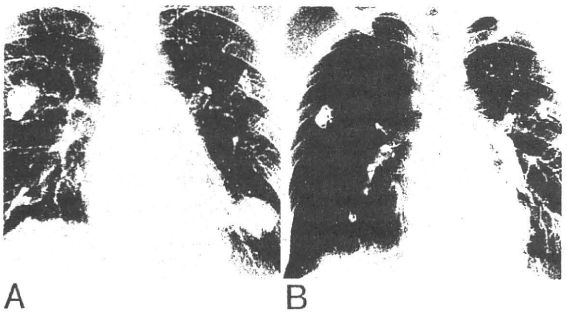

Figure 4 Case 4. (a) Pulmonary angioram showing four PAVMs in both lungs. (b) Pulmonary angiogram after embolization with steel coils showing occlusion of PAVMs in both lungs.

DISCUSSION

The first acount of PAVMs, attributed to Churton,[16] is a pathological report. The name of ROW disease derives from three subsequent authors.[2,17–19] Rendu[18] described familial epistaxis in patients with angiomas of the skin and mucous membranes. Osler[2] presented three cases of lesions with epistaxis and clearly distinguished capillary pathology from other causes of epistaxis that could be attributed to clotting disorders. Finally, Weber[19] described the skin and nasal manifestations of ROW disease. Pulmonary complications were not recognized clinically until Wilkens[20] gave a description of a cyanotic 16-year-old girl who was found to have multiple PAVMs at autopsy. Dines *et al.*[6] reported on 63 cases of PAVMs; 36% with ROW disease. Deaths in the medically treated group were primarily from cerebrovascular accidents. Dines *et al.* later reported on a further 38 cases including 47% with ROW disease. These pooled data indicate a 40% incidence of ROW disease in cases of PAVMs.[3] All reviews have emphasized an autosomal dominant pattern of genetic transmission. However, in at least one case of possible homozygosity, the affected stillborn offspring exhibited extensive angiomatous malformations of the internal organs that were more severe than the clinical findings in the heterozygous parents.[1,17]

Race has been reported as a factor in the prevalence of ROW disease, which is rare in black people and Arabs. In Japan, 144 ROW patients and 126 ROW families have been described and approximately one-third of the ROW patients have been associated with PAVMs.[15] Thus, ROW disease is less rare than previously believed in Japan.

Surgical excision of part or all of the lung was the usual treatment for PAVMs from 1939 until recently.[11,12] Silicone and latex balloons were first introduced for neurosurgical procedures in Europe. Servinenko temporarily occluded 304 different cerebral vessels using this method,[21] although none of his patients were reported to have ROW disease. His work inspired White *et al.* to initiate research with detachable silicone balloons in swine. Since then, White *et al.*[4] have reported a series of 17 patients with 91 PAVMs. Balloon embolization is thus an new important approach to the treatment of PAVMs, and its implications for the reduction of morbidity and mortality in ROW disease are considerable.[22]

Coil embolization has also been applied for PAVMs by Taylor *et al.*[11] More recently, Dutton *et al.*[23] have reported the results of treatment with coil embolization in 53 PAVM patients, concluding that the technique is effective, well tolerated, and associated with few complications. The correct choice of coil size is critical: too small a coil may pass through the venous portion of the malformation into the left atrium and thence into the systemic circulation, potentially with disastrous consequences, while too large a coil may displace the catheter tip from the feeding vessels and risk occlusion of the more proximal normal pulmonary arterial branches. A variety of methods, including the use of calibrated catheters, have been used to measure the feeding vessels supplying the malformation and thus determine the correct coil size.[5,23]

Detachable balloons are preferred by some researchers for the embolization of PAVMs, since these devices, unlike conventional steel coils, can be retrieved if they are too small for the vessel being occluded, and fewer normal vessels are occluded by the balloon technique than the coil technique.[5,22] Balloon embolization does, however, require multiple catheter exchanges for embolization of more than one vessel. Also, when non-polymerizing liquids are used for the balloon inflation, as in our case 1, there is a risk that the balloon will deflate prematurely and migrate into the systemic circulation.[5,19] Finally, when the feeding vessel to a PAVM is particulary large, the length of balloon required to achieve occlusion may compromise the more proximal vessels to the normal lung,[5] whereas the use of steel coils usually preserves

these vessels.[5,21] Thus, we consider metal coil therapy to be an easier and safer technique than detachable balloon therapy for PAVMs associated with ROW disease. However, further prospective clinical studies will be needed to determine the relative merit of the two techniques.

CONCLUSION

PAVMs associated with ROW disease are multiple in occurrence and may appear in succession. Treatment of PAVMs is crucial in ROW disease because the rupture of the PAVM or systemic emboli via PAVMs may be lethal. Percutaneous transcatheter embolization is the procedure of choice for the treatment of PAVMs associated with ROW disease. This technique is safe and well tolerated and is associated with excellent symptomatic and objective improvement. The advantages and disadvantages of embolization by detachable balloons and metal coils have been discussed above. Long-term studies will be needed to determine the risk of recanalization in these treatments.

ACKNOWLEDGEMENTS

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Hereditary Hemorrhagic Telangiectasia (HHT) in Akita Prefecture, Japan

We read with interest the article by Hisamatsu et al (1) indicating the case of Osler-Rendu-Weber disease (hereditary hemorrhagic telangiectasia, HHT) associated with hepatic arteriovenous malformation. HHT was first described in 1864 by Sutton and later recognized and reported by Rendu, Osler, and Weber, and is thus known as Rendu-Osler-Weber disease or Osler-Rendu-Weber disease (2, 3). This is an autosomal dominant disorder characterized by multiple telangiectatic lesions involving the skin and mucous membranes associated with epistaxis and other bleeding complications. HHT has been reported to occur across a wide geographic distribution throughout Europe and North America (2, 3). However, few cases have been reported in Asian countries. Also, there have been no epidemiological studies about the incidence or the prevalence of HHT in Japan.

We have treated 7 families and 10 patients who had pulmonary arteriovenous malformations (PAVMs) since 1978. Ten patients (4 males, 6 females, aged 56±12 years) with HHT were admitted for evaluation and treatment at the Second Department of Internal Medicine at Akita University School of Medicine during from 1978 to 1999. We interviewed their families to obtain precise information. The clinical criterion for the diagnosis of HHT was the presence of any two of the following: recurrent epistaxis, telangiectases elsewhere than in the nasal mucosa, evidence of autosomal dominant inheritance, and visceral involvement (4). Pedigrees of 7 families and family members are shown in the Fig. 1. Fifty-one persons out of 208 family members (24.8%) were diagnosed to be HHT, and 17 HHT patients (8.2%) had PAVMs. The percentage of HHT patients associated with PAVMs was 33.3%, which is close to the percentages (20–30%) that were reported in Europe and North America (2).

HHT has an estimated prevalence of 1 in 2,351 members of the population in the eastern France area of Ain, in 3,500 on the Danish island of Funen, in 5,155 in the Leeward Islands, 1 in 16,500 in Vermont, and 1 in 39,216 in northern England (2, 3). The population of Akita prefecture in 1998 was reported to be 1,221,720. Therefore, if 51 HHT patients at our university are hypothesized to be the total number, the prevalence of HHT in Akita Prefecture is roughly estimated at 1:24,000, a figure close to those reported in Vermont and northern England.

Recently, the condition has been shown to be a family of disorders caused by mutations in various genes, and the genes responsible for two forms have been identified (5, 6). Genetic linkages to HHT have been established to chromosome 9q33-q34 in some families and to chromosome 12q in others (5). This discovery of genetic heterogeneity should bring a re-evaluation of the natural history of these disorders, because the incidence of the many clinical manifestations may vary widely among the various forms. A current multicenter effort is analyzing the correlations between genotype and phenotype (6). Multicenter cooperation may also lead to randomized prospective trials to determine the efficacy of various therapies. The development of a functional assay to provide presymptomatic diagnosis appears possible. The finding that a protein binding transforming growth factor β (TGF-β) has a key role in the disease should help elucidate the pathophysiologic features. Therapeutic advances, including gene replacement, may now be a realistic possibility given the ease of access through the bloodstream to endothelial cells, the target tissue (5, 6). Although the understanding of HHT is expanding rapidly as stated above, there have been no such studies reported so far among Japanese HHT patients. Thus, the national epidemiological survey for HHT and genetic analysis of this disease in Japan is very urgent.

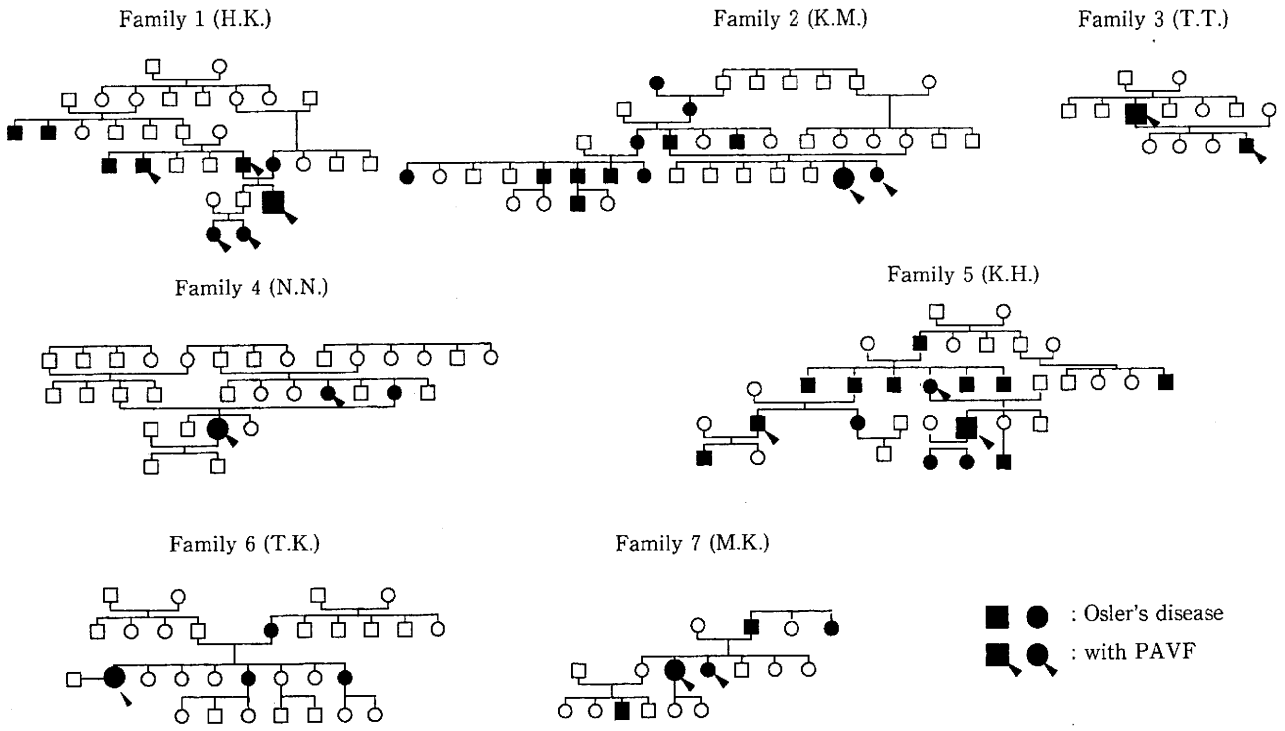

Figure 1. Pedigree of HHT patients in Akita Prefecture. Large symbols indicate the proband of the family. Closed symbols indicate HHT patients, and arrows indicate the patients associated with PAVMs.

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HUMAN MUTATION 19:140–148 (2002)

RESEARCH ARTICLE

Genetic Epidemiology of Hereditary Hemorrhagic Telangiectasia in a Local Community in the Northern Part of Japan

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Communicated by David Yandell

Hereditary hemorrhagic telangiectasia (HHT or Rendu-Osler-Weber syndrome) is an autosomal dominant disorder characterized by aberrant vascular development. We report here a genetic epidemiologic study in a county, A, in the Akita prefecture (population 1.2 million) located in northern Japan. Nine HHT patients who had been referred to tertiary-care hospitals were located in and near the study county. A total of 137 pedigree members were traced of which 81 were alive and 32 were affected by HHT. Complications associated with cerebral or pulmonary arteriovenous malformations were proven in six out of seven families. Linkage analysis in two large families revealed a weak yet suggestive linkage to the *HHT1* locus (encoding *endoglin*; ENG). Three novel mutations were found in four families, all of which led to a frameshift: a G to C transversion at the splicing donor site of intron 3 (Inv3+1 G>C) in one family, one base pair insertion (A) at nucleotide 828 (exon 7) of the *endoglin* cDNA in two large families (c.828–829 ins A), and a four base pair deletion (AAAG) beginning with nucleotide 1120 (exon 8) of the *endoglin* cDNA (c.1120–1123 delAAAG) in one family. The insertion of A in exon 11 (c.1470–1471 insA) mutation found in one family has also been reported in a European family. No *endoglin* gene mutations were found in two families. The population prevalence of HHT in the county was estimated to be 1:8,000–1:5,000, roughly comparable with those reported in European and U.S. populations, which is contradictory to the traditional view that HHT is rare among Asians. We recommend that families with HHT be screened for gene mutations in order that high-risk individuals receive early diagnosis and treatment initiation that will substantially alter their clinical course and prognosis. Hum Mutat 19:140–148, 2002.

KEY WORDS: ACVRL1; ALK1; hereditary hemorrhagic telangectasia; HHT; endoglin; ENG; genetic epidemiology; vascular complications; Japanese

DATABASES:
ENG – OMIM: 131195, 187300 (HHT); GDB: 137193; GenBank: AH006911
ACVRL1 – OMIM: 601284, 600376 (ORW2); GDB:230240; GenBank: AH005451

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