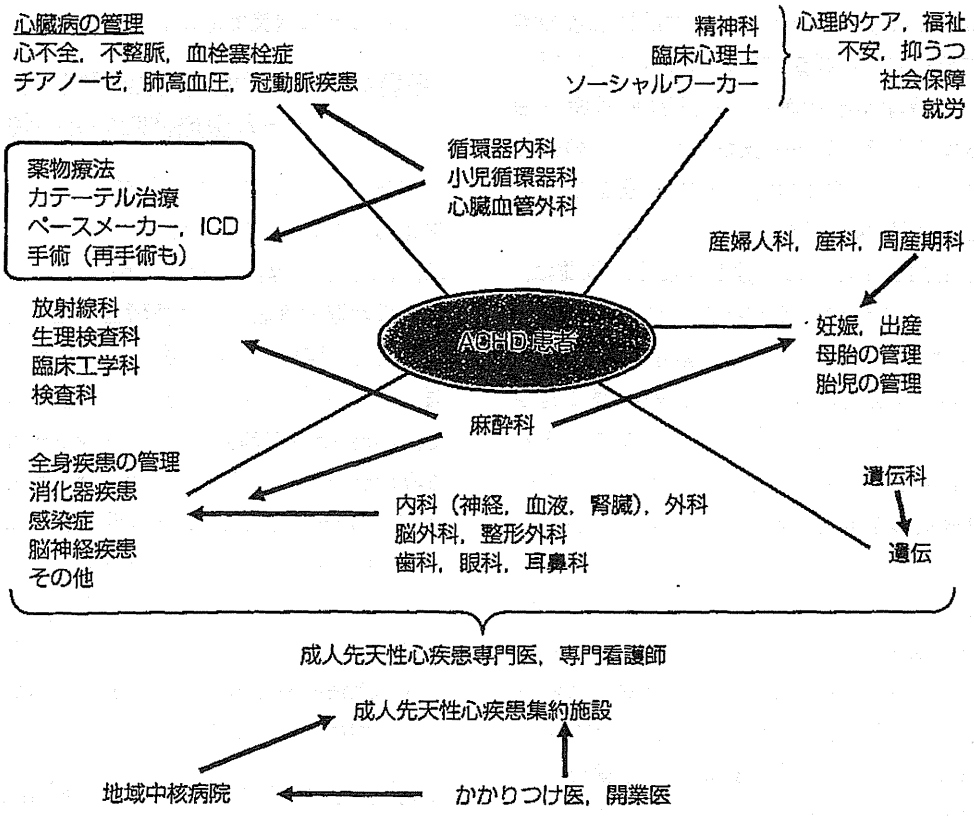

図２　今後の成人先天性心疾患の診療体制

ACHDは定期的な経過観察が必要である。基本的に，重症患者は集約施設で経過観察，それ以外の軽症や中等症とされる患者はかかりつけ医，地域中核病院などでの経過観察を行う。場合により1～2年に一回，あるいは病状悪化時の集約施設への受診が推奨されている。

地域中核病院などで経過観察を行うことが望ましい。新生児，乳児そして小児の時期から，親身に患者のケアを行ってきている開業医も少なくないし，患者もこのような医師のもとでの経過観察を好む。このような患者と医師の親密な関係は，ACHD分野の医療のスタイルとして重要である。しかし，ACHDに特化した問題（不整脈，心不全，肺高血圧，妊娠出産など）が生じた場合は，すぐに集約施設に紹介できる体制を確立することも大切である。集約施設で経過観察をする場合，患者の状態により1～2年に一回，あるいは病状悪化時の集約施設への受診は，患者の状態を保ち，QOLを担保する上で非常に重要である（図2）。

移行診療

1．患者自身の自分の病気や病態の認識

複雑CHD患者は，綿密な経過観察が必要である。しかし，複雑心疾患患者であればあるほど，小児期から多くの点で両親への依存度が高く，自己の病気の病態や今後起こりうる合併症などに対する理解に乏しいことが多い。実際に自分の心疾患の病名や手術内容を知らないことも少なくない。成人期以降も良好なQOLを保ち，罹病率や生命予後を改善させるには，小児循環器科医から成人先天性心疾患外来への移行期間中もしくはそれ以前に，病名や病態の告知，手術歴を含む治療歴，今後起こり得る合併症と対策，日常生活の注意点などを，本人に時間をかけて，繰り返し説明する必要がある[2]。

2．移行時期とACHD診療における小児循環器科医，循環器科医，ACHD専門医の特徴

CHD患者や両親は，生後早くから慣れ親しんできている小児循環器科医に成人期以降も診療を続けてほしいと考えることもが多いが，①根本的にACHD患者は小児ではなく成人であること，②小児循環器科医のマンパワーには限りがあること，③

表3　集約施設でACHDの移行期の経過観察を行う場合の担当医師の特徴

	小児循環器科医	循環器内科医	成人先天性心疾患医
CHDの知識	十分	不十分	十分
成人疾患の知識	不十分	十分	十分
外来	小児科	内科	内科
病棟	小児科	内科	内科
標榜科	違和感	違和感なし	違和感なし
専門医の絶対数	少ない	多い	なし
総合的な診療	行っている	行わない	行なうことが多い
診療方法	両親に話す	本人に話す	本人に話す

小児循環器科医，循環器内科医と成人先天性専門医の特徴を記載した。担当医師のトレーニングを受けた背景が，小児循環器科，循環器内科であるかを問わず，今後は，ACHDを専門的に診る医師，医療スタッフが診療には不可欠である。

小児科医は内科疾患診療の訓練を受けていないことなどから，循環器小児科医が成人患者を診察し続けるには限界がある（表3）。ACHD専門医や循環器内科医へのスムースな移行は，患者の成人期以降の通院拒否（ドロップアウト）につながらないためにも必要である。移行診療の実施時期は患者の病状，年齢，成熟度，病気の理解度にも左右されるが，早い患者では中学に入学する12歳頃より，また遅くとも15歳頃までには，患者本人に病気の説明を開始することが望ましい[2]。高校を卒業して親元を離れ，専門学校や大学に進学するか，就職して独立する可能性のある18歳（もしくは20歳）までには，移行診療を終了するのが理想的である[2]。

患者教育の内容には，将来的な問題点，特に女性患者では，妊娠や出産，避妊に関連した注意事項も含む。思春期には，小児循環器科医が診療を継続しながら成人先天性心疾患外来に紹介し，患者とACHDの専門医師（あるいは循環器内科医）と併診しながら，徐々に循環器内科医への受診頻度を高めることにより移行を進める方法を取る場合もある。この場合，医師の専門性や成人である患者自身の将来に関することを十分に説明することが必要である。小児循環器科医，循環器内科医など医師の側も移行診療の重要性を十分に認識する必要がある[8]。小児科医から内科医への移行医療の問題は，先天性心疾患に限らず，すべての小児慢性疾患の診療分野で起こっている。欧米のように，日本でもこども病院は移行診療および相互診療を行いやすいように，循環器科のある総合病院の近くに設立することが望ましい。

まとめ

ACHDには解決すべき問題は多いが，①ACHD診療に循環器科医が参加する，②多科多職種で構成されるACHDのチーム診療を行える集約施設を全国に設立する，③ACHDの認定医／専門医制度を推進する，④集約施設を中心とし，かかりつけ医，地域中核病院間で病診連携を確立する，⑤患者が成人になるまでに循環器内科やACHD診療専門施設への移行診療を進める，ことなどが必要である。これらの目的のために，日本成人先天性心疾患学会を中心として，循環器科医のこの分野への参加は急激に進んでおり，日本のACHDの将来は明るい[7]。

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巻頭言

成人となった先天性心疾患の診療とその将来

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巻頭言

成人となった先天性心疾患の診療とその将来

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聖路加国際病院特別顧問

先天性心疾患は成人循環器疾患の1分野となっている．中等症から複雑先天性心疾患は，小児期に心臓血管手術を行うが，根治手術ではなく定期的な経過観察が必要な修復手術である．成人先天性心疾患(ACHD)は，年齢とともに，心機能悪化，不整脈，突然死，再手術など心血管系に関する問題を生じる．妊娠，出産，就業，保険，心理的社会的問題などの問題も重要である．この分野は，ACHDを専門に診る医師，看護師を中心とし，循環器内科医，小児循環器科医，心臓血管外科医や各分野の専門医などチーム医療体制を確立する必要がある．日本では1990年代後半の成人先天性心疾患研究会(現在は学会)の発足と同時にACHD診療施設が設立された．ACHDは，成人循環器疾患とは異なる管理方法，診療体制が必要である．2012年に，ACHD診療を行う循環器内科施設グループ「ACHD循環器内科ネットワーク」が立ち上がり，現在，33施設を超える循環器内科が，ACHDの診療を開始している．

日本成人先天性心疾患学会は，学術集会の教育講演，ACHDセミナーを定期的に開き，若手医師，医療従事者の教育に力を入れている．ACHD学会が独自に学術集会を開いているのは日本だけである．日本循環器学会学術委員会に成人先天性心疾患部会が，日本心臓病学会にもACHD設立準備委員会が設けられた．今後は日本成人先天性心疾患学会を中心として，関連各学会，ACHD循環器内科ネットワーク，厚生労働省研究班とともに，ACHD診療への循環器科医の参加と診療体制の確立が進むと予想される．

ACHD患者は小児期から両親への依存度が高く，自己の病気や合併症への理解に乏しい．良好なQOLを保ち，罹病率や生命予後を改善するには，小児循環器科医から成人先天性心疾患医への移行期に，病名や病態の告知，治療歴，合併症，妊娠や出産，日常生活の注意点を本人に説明する移行期診療が必要である．

ACHDの研究面ではハイブリッド治療，複雑心疾患の術後遠隔期の諸問題と突然死予防，妊娠出産登録制度，精神心理的問題など多々あるが，分子レベルでの研究，罹病率，生命予後の改善と突然死予測/予防，再生医療，緩和医療，移行医療，移植医療と人工心臓，社会保障体制，多職種共同研究の推進などは今後の大きな研究課題である．

ACHDは新しい分野であり，海外でも専門とする医師の数が少なく，このため，国際的な交流，協力が盛んである．海外の学会には，世界成人先天性心疾患学会(International Society for ACHD)，Asia Pacific Society for ACHD (APSACHD)，Grown-up CHD (ESC GUCH)などがある．アジアでも，韓国，台湾，タイ，インドなどACHD学会を持つ国が増加している．これらの学会は，相互交流が盛んで，共同研究も進み始めている．

ACHDには，今後，臨床上解決すべき問題は多いが，①循環器科医の参加，②チーム診療を行える集約施設の確立，③認定医/専門医制度の推進，④集約施設，地域中核病院，かかりつけ医間での病診連携の確立，⑤移行診療の推進，⑥登録制度の確立と診療ガイドラインの改訂などが必要である．これらの目標達成のために，日本成人先天性心疾患学会を中心として，関連医師の参加は急激に進んでおり，日本のACHDの将来は明るいと考えている．

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Original Article

Antifungal Susceptibility of *Candida* Isolates at One Institution

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ABSTRACT

Species distribution and antifungal susceptibility of *Candida* isolates at one institution were evaluated. Detection rates of fungi were examined for 5 years between 2007 and 2011. Sensitivities of fungi to amphotericin B, flucytosine, fluconazole, micafungin, itraconazole, and voriconazole were evaluated in blood culture-positive patients. A total of 3,832 fungal isolates were detected, including *Candida albicans* 66.5%, *Candida glabrata* 20.3%, *Candida parapsilosis* 6.2%, *Candida tropicalis* 5.5%, and others 1.5%. Candidemia was diagnosed in 131 patients, and *C. albicans, C. parapsilosis, C. glabrata, C. tropicalis*, and others were present in 42.0%, 27.5%, 16.0%, 8.4%, and 6.1% of these patients, respectively. Voriconazole had the lowest MIC_{90}s against *C. albicans* and *C. parapsilosis* (0.015 and 0.25). Micafungin had a low MIC_{90} against *C. glabrata* and *C. tropicalis*. *C. albicans* was the most common fungus in patients with candidemia. Voriconazole and micafungin were effective against *C. albicans*. Amphotericin B was effective for *C. parapsilosis*, and micafungin showed good efficacy against *C. glabrata* and *C. tropicalis*.

Key words : fungus, antifungal susceptibility, antifungal agents, *Candida*, candidemia

Introduction

Recent developments in medical technology have improved the survival of patients with severe tissue damage, those who undergo complex surgery, and those with severe circulatory failure. However, deep mycosis in these patients may induce opportunistic infections that may be difficult to diagnose and treat. The incidence of deep mycosis has increased in surgery, ambulatory care, and intensive care units, and is commonly treated with antimicrobial agents. *Candida* mycosis is treated with empirical therapy using azole antifungal drugs including fluconazole, and the prognosis is good. However, *Candida albicans* may show low sensitivity or resistance to these drugs, and non-*albicans Candida* species are also increasingly being isolated[1–5].

In this study, the detection rate of deep mycosis, the drug sensitivity of the causal species, and the use of antifungal drugs were examined at the National Cerebral and Cardiovascular Center (NCVC). The goals of the study were to establish the antifungal drug sensitivity of *Candida* strains isolated in the center and to identify appropriate agents for treatment of deep mycosis.

Materials and Methods

The detection rates of fungi at the NCVC were determined for 5 years between January 2007 and December 2011. Sensitivities of fungi to amphotericin B, flucytosine, fluconazole, micafungin, itraconazole, and voriconazole were examined in blood culture-positive patients. The NCVC is located in

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Table 1. Yearly changes of species distribution of 3,832 fungi detected at the National Cerebral and Cardiovascular Center from 2007 to 2011

Species	Number. of isolates					
	2007	2008	2009	2010	2011	Total (%)
C. albicans	461 (70.4)	457 (72.9)	350 (65.2)	555 (71.2)	725 (58.8)	2,548 (66.5)
C. glabrata	128 (19.5)	133 (21.2)	119 (22.2)	131 (16.8)	265 (21.5)	776 (20.3)
C. parapsilosis	23 (3.5)	24 (3.8)	31 (5.8)	46 (5.9)	115 (9.3)	239 (6.2)
C. tropicalis	30 (4.6)	12 (0.9)	34 (6.3)	36 (4.6)	100 (8.1)	212 (5.5)
C. krusei	6 (0.9)	1 (0.2)	1 (0.2)	2 (0.3)	13 (1.1)	23 (0.6)
C. lusitaniae	1 (0.2)	—	—	7 (0.9)	11 (0.9)	19 (0.5)
C. guilliermondii	6 (0.9)	—	2 (0.4)	2 (0.3)	5 (0.4)	15 (0.4)
Total	655	627	537	779	1,234	3,832

All data are shown as a number with the percentage for each year shown in parentheses.

an urban area in Japan, and specializes in surgical treatment of cardiovascular diseases, including cerebrovascular and internal injuries. The facility also manages pregnancy and delivery for women with maternal cardiac diseases. The NCVC has 612 beds and about 10,000 new hospital stays each year. The average hospital stay is 17 days, and 650 and 190 heart surgeries are performed annually for adults and infants, respectively. Ten heart transplantations are performed each year.

Culture media

CHROMagar Candida (CHROMagar, Paris, France) was purchased as a powder. CHROMagar is composed (per liter) of 10 g peptone, 20 g glucose, 15 g agar, 0.5 g chloramphenicol, and 2 g chromogenic mix. The medium was prepared according to the manufacturer's instructions and dispensed in petri dishes (20 m*l* in a 90-mm diameter dish).

Identification of fungus species

Clinical specimens from cases with suspected myconal infections were inoculated onto CHROMagar and incubated at 37℃ for 48 h. Macroscopic identification was performed based on the color and shape of the grown colonies. Strains without typical characteristics on the CHROMagar were identified with a ID 32℃ Yeast Identification System (bioMerieux S. A.), using colonies on the CHROMagar prepared using the solution provided with this system.

Determination of sensitivity to antifungal drugs

The microdilution method was used to study drug sensitivity, using an Antifungal Susceptibility Test for Yeast (Kyokuto Pharmaceutical Industrial Co.) that complied with Clinical and Laboratory Standards Institute (CLSI) criteria. M27-A3 was used to determine the minimum inhibitory concentration (MIC) of amphotericin B (measurable concentration range 0.03-16 μg/m*l*), flucytosine (0.125-64 μg/m*l*), fluconazole (0.125-64 μg/m*l*), micafungin (0.03-16 μg/m*l*), itraconazole (0.015-8 μg/m*l*), and voriconazole (0.03-16 μg/m*l*). Sensitive (S), sensitive dose-dependent (S-DD), intermediate (I), and resistant (R) responses to flucytosine, fluconazole, and itraconazole were evaluated using CLSI M27-S3 criteria[6].

The study was exempted from Committee on Human Research approval (National Cerebral and Cardiovascular Center) because there no longer exists a key or code sheet relating the individuals' identities to their private health information.

Results

A total of 3,832 patients had a detected fungal infection in the 5-year period from 2007 to 2011 in the NCVC, including 2,548 patients with *C. albicans* (66.5%), 776 with *C. glabrata* (20.3%), 239 with *C. parapsilosis* (6. 2%), and 212 with *C. tropicalis* (5.5%) (Table 1). Non-*albicans* infections accounted for 33.5% of cases. The location and materials of isolated *Candida* species are shown in Table 2.

The number of blood culture performed were 2,819, 3,306, 2,900, 3,797, 4,239 in 2007, 2008, 2009, 2010, and 2011, respectively. The number and percentages of patients with fungemia caused by *C. albicans, C. parapsilosis, C. glabrata, C. tropicalis, Candida lusitaniae, Candida guilliermondii*, and *Candida krusei* were 55 (42.0%), 36 (27.5%), 21

Table 2. Location and materials of isolated *Candida* species

Species	Sputum	Urogenital	Stool	Intra-body material	Blood	Skin	Others	Total
C. albicans	1,309 (72.8)	800 (62.7)	150 (56.0)	113 (58.9)	55 (42.0)	81 (79.4)	40	2,548
C. glabrata	291 (16.2)	333 (26.1)	87 (32.5)	25 (13.0)	21 (16.0)	10 (9.8)	9	776
C. parapsilosis	56 (3.1)	77 (6.0)	8 (3.0)	38 (19.8)	36 (27.5)	11 (10.8)	13	239
C. tropicalis	123 (6.8)	49 (3.8)	17 (6.3)	11 (5.7)	11 (8.4)		1	212
C. krusei	13 (0.7)	4 (0.3)	4 (1.5)		1 (0.8)		1	23
C. lusitaniae	4 (0.2)	5 (0.4)	2 (0.8)	2 (1.0)	5 (3.8)		1	19
C. guilliermondii	2 (0.1)	8 (0.6)		3 (1.6)	2 (1.5)			15
Total	1,798	1,276	268	192	131	102	65	3,832

All data are shown as a number with the percentage in parentheses. Sputum includes respiratory related materials. Intra-body materials include catheters and drainage tube. Aspiration fluid indicates ascites, pleural effusion, and pericardial effusion.

Table 3. Yearly changes of species distribution of 131 *Candida* blood isolates detected at the National Cerebral and Cardiovascular Center from 2007 to 2011

Species	Number (%) of isolates					
	2007	2008	2009	2010	2011	Total
C. albicans	7 (41.1)	7 (43.8)	8 (44.4)	25 (59.5)	8 (25.0)	55 (42.0)
C. parapsilosis	2 (11.8)	4 (25.0)	3 (16.7)	11 (25.0)	16 (44.4)	36 (27.5)
C. glabrata	3 (17.7)	3 (18.8)	4 (22.2)	5 (11.4)	6 (16.7)	21 (16.0)
C. tropicalis	4 (23.5)	1 (6.3)	2 (11.1)	2 (4.6)	2 (5.6)	11 (8.4)
C. lusitaniae	—	1 (6.3)	—	1 (2.3)	3 (8.3)	5 (3.8)
C. guilliemondii	1 (5.9)	—	1 (5.6)	—	—	2 (1.5)
C. krusei	—	—	—	—	1 (2.8)	1 (0.8)
Total	17	16	18	44	36	131

All data are shown as a number with the percentage for each year in parentheses.

(16.0%), 11 (8.4%), 5 (3.8%), 2 (1.5%), and 1 (0.8%), respectively (Table 3), with 58% of the cases of fungemia caused by a non-*albicans* species.

Drug sensitivity

Data for the sensitivity of fungi to amphotericin B, flucytosine, fluconazole, micafungin, itraconazole, and voriconazole are shown in Table 4. Amphotericin B was not classified into S, S-DD, I, and R categories in the CLSI 2009 criteria.

The MIC_{90} of voriconazole against *C. albicans* (0.015) was the lowest among the 6 antifungal drugs, followed by micafungin (0.06), flucytosine (0.25), itraconazole (0.25), amphotericin B (0.5), and fluconazole (0.5). However, none of the 55 patients with candidemia caused by *C. albicans* showed resistance in the CLSI criteria (flucytosine $\geq$ 32, fluconazole $\geq$ 64, itraconazole $\geq$ 1, voriconazole $\geq$ 4). Of these 55 cases, 46 (83.6%) were S-DD to itraconazole and all 55 were sensitive to the other 5 antifungal drugs.

The MIC_{90} of voriconazole and against *C. parapsilosis* (0.125) was also the lowest among the antifungal drugs, followed by flucytosine (0.25), amphotericin B (0.5), itraconazole (1), micafungin (2), and fluconazole (16). The resistance rates of *C. parapsilosis* to fluconazole and itraconazole were 5.6% and 25.0%, respectively. The percentages of patients with S ($\leq$ 0.125), S-DD (0.25–0.5), and R ($\geq$ 1) responses were 27.8%, 47.2%, and 25.0%, respectively, for itraconazole. The percentages of patients with S ($\leq$ 8), S-DD (16–32), and R ($\geq$ 64) responses were 83.3%, 11.1%, and 5.6%, respectively, for fluconazole.

The MIC_{90} of micafungin against *C. glabrata*

Table 4. Antifungal susceptibilities of *Candida* blood isolates determined by microdilution method after 48 h of incubation

Species (number of isolates)	Antifungal agent	MIC (μg/ml) [a] range	50%	90%	% Resistant[b]
C. albicans (55)	Amphotericin B	0.13-1	0.5	0.5	—
	Flucytosine	< 0.13-1	0.13	0.25	0
	Fluconazole	< 0.13-2	0.25	0.5	0
	Micafungin	< 0.03-0.06	< 0.03	0.06	—
	Itraconazole	0.03-0.5	0.13	0.25	0
	Voriconazole	< 0.015-0.5	< 0.015	0.015	0
C. parapsilosis (36)	Amphotericin B	0.13-1	0.25	0.5	—
	Flucytosine	< 0.13-0.5	0.25	0.25	0
	Fluconazole	0.5-64	1	16	5.6
	Micafungin	0.25-2	0.5	2	—
	Itraconazole	0.13-2	0.25	1	25
	Voriconazole	< 0.015-1	0.03	0.125	0
C. glabrata (21)	Amphotericin B	0.13-1	0.5	1	—
	Flucytosine	< 0.13-0.25	< 0.13	0.13	0
	Fluconazole	8-> 64	16	64	19.1
	Micafungin	< 0.03-0.06	< 0.03	0.06	—
	Itraconazole	1-> 8	2	8	100
	Voriconazole	0.25-> 8	0.5	1	14.3
C. tropicalis (11)	Amphotericin B	0.13-1	0.25	0.5	—
	Flucytosine	0.13-4	0.25	0.25	0
	Fluconazole	1-> 64	8	> 64	36.4
	Micafungin	0.06-2	0.06	0.13	—
	Itraconazole	0.25-> 8	4	> 8	72.7
	Voriconazole	0.13-0.5	0.25	0.5	0

[a] 50% and 90% minimum inhibitory concentrations: MIC_{50} and MIC_{90}, respectively.
[b] Percentage of resistant strains according to CLSI breakpoints (CLSI M27-S3 2009)
CLSI: Clinical and Laboratory Standards Institute; "-" indicates break point is not established in CLSI M27-S3

(0.06) was the lowest among the antifungal drugs, followed by flucytosine (0.13), amphotericin B (1), and voriconazole (1). The resistance rate to voriconazole was 14.3%. The drug resistance rates of itraconazole and fluconazole were 100% and 19.1%, respectively.

The MIC_{90} of micafungin against *C. tropicalis* (0.13) was significantly lower than those for other drugs, followed by amphotericin B and voriconazole (both 0.5). The resistance rate of *C. tropicalis* against voriconazole was 0%.

Discussion

131 *Candida* strains isolated from blood at the NCVC from 2007 to 2011 showed species distribution, *C. albicans* 42.0%, *C. parapsilosis* 27.5%, *C. glabrata* 16.0%, *C. tropicalis* 8.4%, and *C. krusei* 0.8%. Our data and the results of a national surveillance study indicate that *C. albicans* is still the major causal fungus of candidemia in Japan. In *C. albicans* no isolate with resistance to fluconazole $\geq$ 64 μg/ml was found in this study[7]. The 90%MIC was 0.5 μg/ml and the isolate with

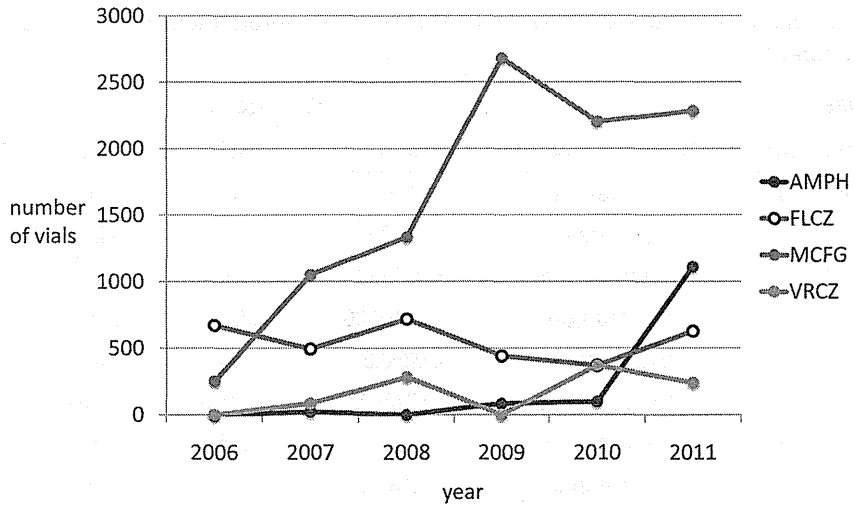

Fig. 1. Use of antifungal agents. Fluconazole was the most commonly used antifungal drug in 2006, whereas micafungin was most commonly used from 2007 to 2011. Use of AMPH increased in 2011, which reflects the increase of fungemia caused by *C. parapsilosis*. AMPH: amphotericin B, FLCZ: fluconazole, MCFG: micafungin, VRCZ: voriconazole.

lowest susceptibility required 2 μg/ml. These findings led us to use an antifungal susceptibility-based management strategy in NCVC for treatment for known *C. albicans* infection in which fluconazole is the first line antifungal drug.

The rates of resistance of *C. glabrata* to itraconazole and fluconazole (100% and 20%) were greater than those (56.3% and 5.2%) in Takakura et al[7]. High rates of resistance to itraconazole for *C. glabrata* detected in the bloodstream were also found by Myoken (100%, 8/8) [8] and St-Germain et al. (83.3%, 65/78) [9]. In our study, none of the 25 *Candida* isolates with reduced susceptibility to fluconazole (MIC $\geq$ 16 μg/ml) was susceptible to itraconazole (MIC $\leq$ 0.12 μg/ml). However, Pfaller et al. suggested that MICs of $\leq$ 1 μg/ml may better reflect 'susceptibility' in invasive candidiasis, due to the higher serum concentrations achievable with the new nanocrystal intravenous formulation of itraconazole[10]. Given this new threshold, 40.0% of our isolates with reduced susceptibility to fluconazole would be considered susceptible to itraconazole. Furthermore, our observations are similar to those of Pfaller et al., with all four of our *C. glabrata* isolates that were resistant to fluconazole also showing resistance to itraconazole.

The higher resistance rate of *C. tropicalis* to fluconazole (36.4%) compared to reports from the USA (6.2%) and Spain (16.6%) is another characteristic of non-*albicans* candidemia in this study[11,12]. We attribute this high resistance to the consistent and high frequency use of fluconazole in our facility. Interestingly, for each case of fluconazole-resistant non-*albicans* candidemia (4 isolates of *C. glabrata*, and 4 isolates of *C. tropicalis*), micafungin showed high sensitivity and can be regarded as the first choice for treatment of fluconazole-resistant *C. glabrata* and *C. tropicalis*. Voriconazole showed no resistance to *C. tropicalis* and may be used as the second choice for these isolates in our hospital; however, voriconazole showed a resistance rate of 43.5% in a national survey[7]. This discrepancy suggests that the susceptibility of each species of *Candida* differs from hospital to hospital, due to the different disease backgrounds and treatments at each center. This indicates that antifungal drug susceptibility at each facility should be considered in the selection of antifungal drugs.

In this study, the greatest number of fungi in the bloodstream was detected in 2011 and the incidence of the disease caused by *C. parapsilosis* (n = 16) was the highest in the same year. The incidence of candidemia caused by *C. albicans* gradually decreased in the study period. We attribute this increase of *C. parapsilosis* to the increase in operations for candidates for heart transplantation and for neonates with congenital heart diseases. These immunologically compromised patients underwent treatments including central line management, which is a known risk

factor for *C. parapsilosis*. This increase in *C. parapsilosis* caused a temporary increase in use of amphotericin B in 2011 (Fig. 1). The selection of this drug for *C. parapsilosis* has turned out to be appropriate because in this study fluconazole showed a resistance rate of 5.6% and a MIC_{90} with micafangin that was as high as 2.0 μg/ml. The MIC_{90} of voriconazole was 0.125, which makes this drug the second choice for *C. parapsilosis* in the NCVC.

We introduced micafungin for treatment of deep mycosis in 2004. By 2006, micafungin accounted for 27% of all antifungal drugs used in the NCVC and from 2009 to 2011 this rate reached 70%. This increased use has occurred because micafungin is an echinocandin that has a broad antifungal spectrum and exhibits good activity against azole antifungal drug-resistant strains. Micafungin is effective in fungal cell lines and several reports have shown excellent tissue penetration and clinical effects[13, 14]. Thus, micafungin has been most commonly used at the NCVC since 2007, including preservational use for immunocompromised patients, such as those undergoing cardiac transplantation or in extremely low-birthweight infants in the NICU. However, several clinical isolates of *Candida* with low resistance to echinocandin antifungal drugs have been described and care is taken regarding this issue at the NCVC[15–18]. The mechanism of this reduced sensitivity involves a mutation in FksIp, which is a 1,3β-D-glucan synthase subunit of the target enzyme of echinocandins[15–18]. No strains with reduced sensitivity to micafungin were found in this study. However, as clinical use of the drug continues to increase, particular attention should be paid to the sensitivity of clinical isolates to micafungin.

C. lusitiniae is an infrequent cause of fungemia, but the rate obtained in this study (3.8%) was 6.8 times higher than that in Takakura[7] and Minari et al[19]. The reported underlying conditions for patients with deep seated *C. lusitaniae* infections are malignancy 53%, neuropenic 35%, receiving broad-spectrum antibiotics 27%, receiving long-term corticosteroid therapy 16%, and having a central venous catheter 27%[20]. Although fungemia is the most common type of *C. lustaniae* infection (80%), primary infection focuses were identified in 20% of cases[20]. These included endocarditis, infection of a left ventricular device, meningitis, chorioamnionitis, peritonitis, abdominal abscess, and cutaneous infection, and most of these diseases are treated at our center. These facts may be related to the higher detected rate of *C. lustaniae* fungemia at our institution. *C. tropicalis* and *C. krusei* are likely to cause deep mycosis in patients with hematologic tumors undergoing digestive tract surgery, but this type of surgery is not performed at the NCVC. This may explain the low incidence of fungemia at the NCVC due to these species[2–4].

In summary, it is important to comprehend the susceptibility for antifungal drug and distribution of each *Candida* isolate of each hospital in selection of antifungal drug, due to the different disease backgrounds and treatments at each center.

Limitations

The sample population was small in this study. In particular, only 11 patients had *C. tropicalis*, which is the minimum required to calculate MIC, and further validation of this result is required. Drug sensitivity may vary depending on the actual treatment in medical institutions, in particular regarding use of the antifungal drug. The NCVC is a specialized center for internal medicine and cardiovascular surgery in patients with cardiovascular disorders or cerebrovascular accident, in contrast to the roles of secondary or tertiary hospitals for general patients. Therefore, it is important to study the drug sensitivity of fungi and measures to be taken against infections in centers such as the NCVC, in which immunocompromised patients are treated, including those undergoing cardiac transplantation, even if the study population is small.

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Conflict of Interest Statement

None of the authors has a conflict of interest regarding the work in this study.

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Pregnancy-associated Intracranial Hemorrhage: Results of a Survey of Neurosurgical Institutes across Japan

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Background: Pregnancy-associated hemorrhagic stroke is considered a serious complication. Although coagulopathy, pregnancy-induced hypertension, eclampsia, and other systemic complications have been emphasized, pre-existing cerebrovascular diseases (CVDs) have not been fully analyzed. To clarify the role of these vascular lesions more in detail, the Japan Neurosurgical Society conducted a nationwide survey on all the neurosurgical institutes across Japan. *Methods:* This 2-year survey focused on hemorrhagic stroke occurring in pregnancy, delivery, and puerperium. Clinical data based on retrospective chart review were obtained through a questionnaire and analyzed according to the time of onset, underlying CVDs, obstetric systemic complications, therapeutic approaches, and maternal and neonatal prognoses. *Results:* The survey identified 97 hemorrhagic strokes that were associated with pregnancy. Baseline CVDs responsible for hemorrhage were detected in 54 cases (55.7%), among which 47 lesions (87.0%) had been undiagnosed before stroke onset. The detection rate of baseline CVDs before the 32nd week of gestation was significantly higher than that after the 32nd week (90.0% versus 53.3%, $P = .0017$). Arteriovenous malformations (AVMs) were the most frequent CVDs causing intracranial hemorrhage, occurring at 1.8 times the frequency of ruptured aneurysms during pregnancy. Poor outcomes, including 10 deaths, were seen in 36.1% of the cases despite aggressive treatment. *Conclusion:* Pregnancy-associated hemorrhagic strokes frequently concealed baseline CVDs, especially when they occurred before the 32nd week of gestation. AVMs were the predominant bleeding source. For appropriate treatment, therefore, close examination for cerebral vascular lesions is essential when a pregnancy-associated hemorrhagic stroke is encountered. **Key Words:** Pregnancy—stroke—intracranial hemorrhage—arteriovenous malformation—cerebral aneurysm—moyamoya disease.
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Introduction

Pregnancy-associated hemorrhagic stroke is well recognized as a serious complication.[1,2] In previous studies conducted mainly by neurologists and obstetricians, systemic obstetric complications including coagulopathies, pregnancy-induced hypertension, and eclampsia were identified as the causes of hemorrhage.[2-7] Pre-existing cerebrovascular diseases (CVDs) such as cerebral aneurysms and arteriovenous malformations (AVMs) were also reported,[4,8] but their incidence and treatments were not fully analyzed. The Japan Neurosurgical Society, therefore, set out to conduct a survey of neurosurgical institutes across Japan regarding pregnancy-associated hemorrhagic stroke with a special focus on identifying underlying CVDs.

Methods

This study is a retrospective analysis based on the clinical chart review in each neurosurgical institute and was

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conducted in 2 phases (primary and secondary surveys) in 2012 as an official project of the Japan Neurosurgical Society. The society has 109 main training institutes across Japan under which 755 affiliated local training institutes participate in providing neurosurgical services. The target of the primary survey was all strokes occurring during pregnancy, delivery, and puerperium (no later than 6 weeks after delivery) that were treated in these institutes between January 2010 and December 2011. In the primary survey, all 109 main training institutes were assigned to compile the number of pregnancy-associated strokes treated in their own hospitals or affiliated local training institutes during the earlier mentioned period. The results were e-mailed to the survey office without any clinical information, and only the e-mail address of the corresponding physician in each case was provided. In the secondary survey, a questionnaire requesting detailed clinical information on each case was e-mailed to each corresponding physician and returned to the survey office without any personally identifying information attached. The clinical information included stroke type and time of stroke onset (gestational age or time after delivery), causes of hemorrhage, types of underlying CVDs, types of obstetric systemic complications, therapeutic procedures for strokes, methods of delivery, and maternal and neonatal prognoses.

Feedback on the primary survey was obtained from 102 (93.6%) main training institutes covering 729 affiliated local training institutes. The survey office sent secondary survey questionnaires to the 126 attendant physicians who had declared their experience with pregnancy-associated stroke and received feedback from 100 physicians (79.4%). After determining the eligibility of each case and eliminating duplications resulting from patient transfer between institutes, the authors extracted 134 cases. These strokes were divided into 97 hemorrhagic strokes (intracerebral or subarachnoid hemorrhage) and 37 other strokes (eg, cerebral arterial infarction or venous infarction), and the former 97 cases were submitted for the further analysis. Intracranial hemorrhage was confirmed by computed tomography (CT) or magnetic resonance (MR) imaging in all cases, and bleeding sources were further examined by MR angiography, digital subtraction angiography, or CT angiography except for a few cases of early death that could not allow further examinations.

Statistical Methods

The data were presented as frequency or means within a standard deviation. Fisher exact probability test and Mann–Whitney *U* test were applied to categorical data. All analyses were performed with Statcel 3 software (OMS Publishing, Inc., Tokorozawa, Japan). Prognosis of the patients was expressed with the modified Rankin Scale (mRS)[9] at discharge.

Table 1. *Demographics of patients with pregnancy-associated hemorrhagic stroke*

	n = 97 (100%)
Mean age (y)	32.2 ± 5.4
Timing of onset	
During pregnancy	
Number of cases	60 (61.9%)
Mean gestational age at onset (wk)	27.7 ± 10.1
At delivery	
Number of cases	13 (13.4%)
Mean delivery weeks	38.4 ± 3.7
Puerperium	
Number of cases	24 (24.7%)
Time after delivery	
<24 h	8
1-3 d	4
3-7 d	3
8-42 d	8
Unknown	1

Results

Patient Demographics

Table 1 summarizes the patient demographics. Among the all 97 hemorrhagic strokes, 60 (61.9%) occurred during pregnancy, 13 (13.4%) at delivery, and 24 (24.7%) during puerperium. Mean gestational age at the onset of hemorrhage during pregnancy was 27.7 ± 10.1 weeks.

Causes of Hemorrhage in Each Period

Figure 1, A shows the causes of hemorrhagic stroke throughout all periods (pregnancy, delivery, and puerperium). Baseline CVDs responsible for hemorrhage were detected in 54 cases (55.7%). Among all vascular lesions, AVMs are the most frequent cause of hemorrhage, followed by cerebral aneurysms and moyamoya disease. Another 3 lesions were also detected, including 2 cavernous malformations and 1 hemorrhage from the vasculature of an intraparenchymal tumor. Of all the detected CVDs, only 7 lesions (13.0%) had been diagnosed before pregnancy, and 47 lesions (87.0%) including all the aneurysms, 92.0% of AVMs, and 60.0% of moyamoya diseases had remained undiagnosed before stroke onset. Fourteen obstetric complications were identified, including pregnancy-induced hypertension, HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, eclampsia, and disseminated intravascular coagulation. Because 2 of these complications were accompanied by bleeding from the AVM and moyamoya disease, they were categorized as "baseline CVDs," and the other 12 cases were categorized as "obstetric complication" in Figure 1. The cause could not be determined in 31 cases (32.0%). Figure 1, B illustrates the causes of hemorrhage in each period. The CVD detection rate was

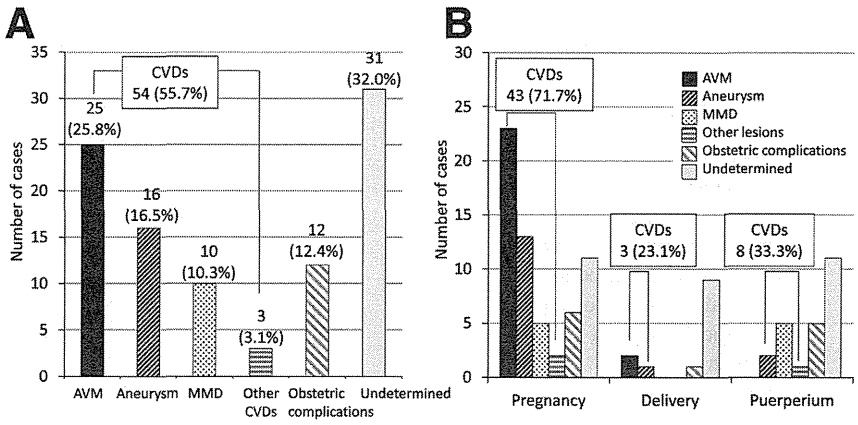

Figure 1. *(A) Causes of hemorrhagic stroke throughout all periods (pregnancy, delivery, and puerperium). (B) Causes of hemorrhagic stroke in each period. Abbreviations: AVM, arteriovenous malformation; CVDs, cerebrovascular diseases; MMD, moyamoya disease.*

71.7% for hemorrhage during pregnancy, 23.1% at delivery, and 33.5% during puerperium. Twenty-three of 25 AVM ruptures (92.0%) were detected during pregnancy, and none were detected during puerperium. Aneurysmal rupture occurred in all periods, but 13 of 16 ruptures (81.3%) were detected during pregnancy. All 6 hemorrhages related to obstetric complications were seen after the 32nd week of gestation.

Gestational Age at Onset and Cause of Hemorrhage during Pregnancy

Figure 2 shows the gestational age at onset of hemorrhagic stroke during pregnancy. Hemorrhagic strokes remarkably increased in number at a later gestational age. Although hemorrhagic strokes before and after the 32nd week of gestation were equal in number (30 cases each), the detection rate of baseline CVDs reached 90.0% (27 of 30) before the 32nd week of gestation, which was significantly higher than that after the 32nd week (53.3%, $P = .0017$ in Fisher exact probability test). Hemorrhagic stroke without baseline CVDs occurred significantly later than that with CVDs (mean 33.7 ± 8.7 weeks versus 25.3 ± 9.6 weeks, respectively; $P < .001$ in Mann–Whitney U test).

Figure 3 compares AVMs and cerebral aneurysms in terms of the gestational age at the onset of hemorrhage. The mean ages at the onset of AVM rupture and aneurysmal rupture were 24.6 ± 9.2 and 27.4 ± 10.4 weeks of gestation, respectively. More specifically, 13 of the 23 AVM ruptures (56.5%) occurred during the latter half (after the 22nd week) of pregnancy, whereas 10 of the 13 aneurysmal ruptures (76.9%) occurred during that same period. Although not statistically significant, aneurysmal rupture had a greater tendency to occur during the latter half of pregnancy than did AVM rupture ($P = .195$, Fisher exact probability test).

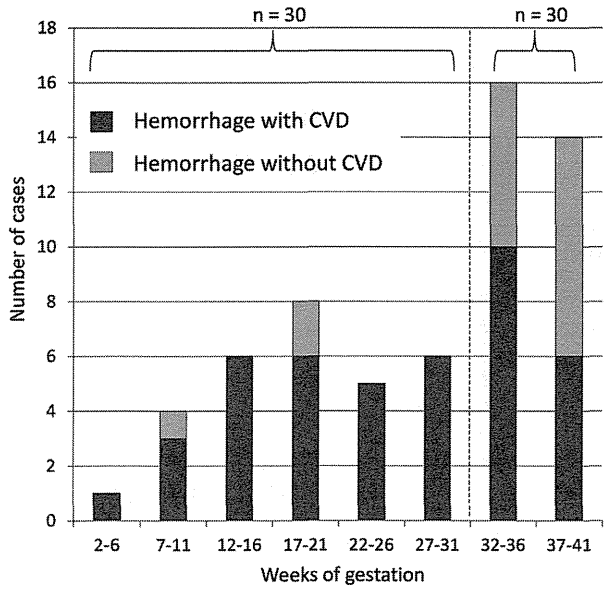

Figure 2. *Distribution of hemorrhagic strokes with and without determined baseline. CVDs by gestational age at onset. Abbreviation: CVD, cerebrovascular disease.*

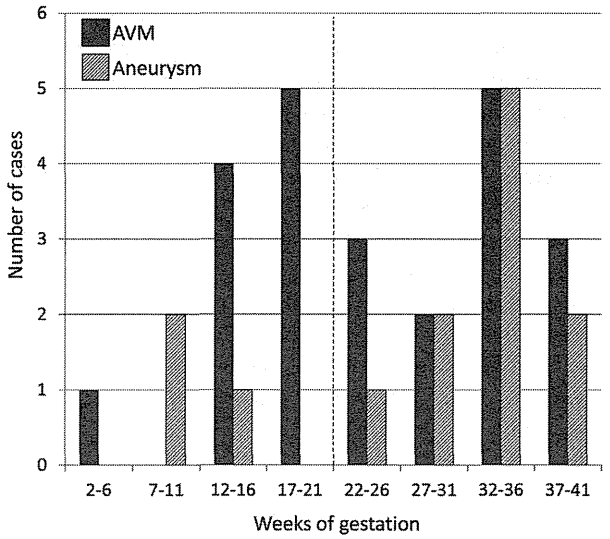

Figure 3. *Distribution of hemorrhagic strokes caused by AVMs and aneurysms by gestational age at onset. Abbreviation: AVM, arteriovenous malformation.*

Table 2. *Therapeutic approaches for pregnancy-associated hemorrhagic stroke*

AVM (n = 25)		
Emergent surgery	15	
Nidus removal		8
Hematoma removal		6
Ventricular drainage		1
Delayed surgery (nidus removal)	2	
Surgery in unknown period (nidus removal)	2	
Embolization in unknown period	1	
Nonsurgical treatment	4	
Unknown	1	
Aneurysm (n = 16)		
Emergent neck clipping	11	
Emergent embolization	4	
None (dead on arrival)	1	
Moyamoya disease (n = 10)		
Emergent surgery	3	
Hematoma removal		1
Ventricular drainage		2
Nonsurgical treatment	7	
Other CVDs (n = 3)		
Emergent hematoma removal	1	
Nonsurgical treatment	2	
Hemorrhage without baseline CVDs (n = 43)		
Emergent surgery	16	
Hematoma removal		10
Ventricular drainage		6
Nonsurgical treatment	27	

Abbreviations: AVM, arteriovenous malformation; CVDs, cerebrovascular diseases.

Therapeutic Approaches and Modes of Delivery

Table 2 summarizes the therapeutic approaches applied to hemorrhagic stroke. Among all cases, 55 (56.7%) required surgical treatment (direct surgery or endovascular surgery) and at least 50 (51.5%) were performed emergently. Eight of 25 AVMs were emergently removed by craniotomy, whereas in the other 7 cases hematoma removal or ventricular drainage was performed without nidus resection. All the aneurysms were emergently clipped or embolized except for 1 case found to be dead on arrival.

Figure 4 shows the methods of delivery adopted in 60 cases of hemorrhagic stroke during pregnancy. Before the 22nd week, induced abortion was selected in 36.8% of the cases, whereas gestation was continued until the elective delivery in 52.6%. When hemorrhage occurred after the 32nd week, 90% of the patients underwent emergent delivery, 96.3% of which were carried out by cesarean section.

Clinical Outcomes of Patients and Children

Figure 5 illustrates the maternal clinical outcomes. Poor outcome (mRS score at discharge ≥ 3) was observed in 35 patients (36.1%). Fatal cases totaled 10,

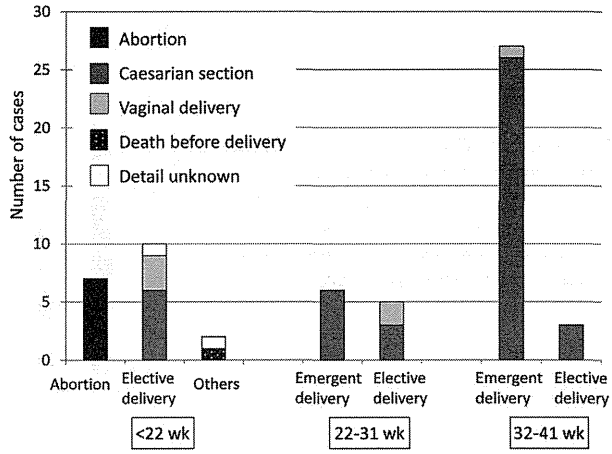

Figure 4. *Methods of delivery adopted after the onset of hemorrhagic stroke during pregnancy.*

making the mortality rate to be 10.3%. Hemorrhage without baseline CVDs showed a higher rate of poor outcome (mRS score ≥ 3) than did that associated with detected CVDs (41.9% and 32.1%, respectively), but the difference was not statistically significant (P = .22, Fisher exact probability test).

Analysis of the prognosis for the children revealed that 81 (83.5%) were normal, whereas 1 (1.0%) had some sequelae and 1 (1.0%) died with the mother. There were 8 cases of abortion (8.2%): 7 were forced abortions after stroke at an early gestational age and 1 was an elective abortion followed by a fatal hemorrhage within 24 hours postpartum. Prognosis of 6 (6.2%) children was not reported.

Discussion

Pregnancy-associated intracranial hemorrhage is a rare but potentially devastating event. A large population-

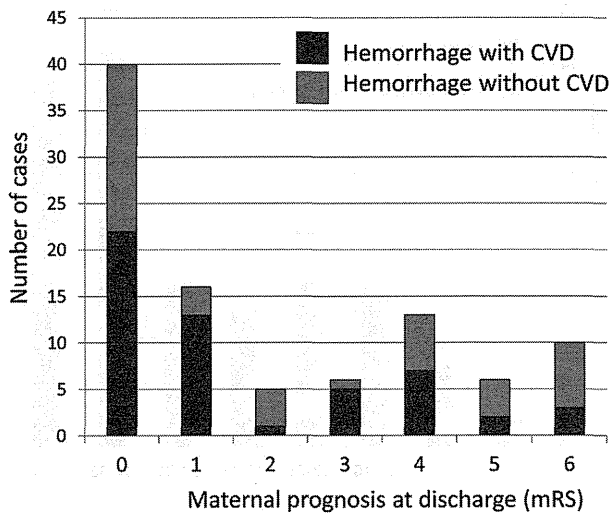

Figure 5. *Maternal outcomes after hemorrhagic stroke with and without determined baseline CVDs. Abbreviations: CVD, cerebrovascular disease; mRS, modified Rankin Scale.*

Table 3. *Recent studies on pregnancy-associated hemorrhagic stroke*

Reference	Country	Total number	Causes of hemorrhage					Rate of CVDs (%)
			AVM	AN	MMD	Other CVDs	No CVD	
Simolke et al[13]	United States	6	1	1	0	0	4	33.3
Sharshar et al[12]	France	16	2	2	0	2	10	37.5
Kittner et al[5]	United States	14	3	0	0	0	11	21.4
Witlin et al[14]	United States	6	1	2	0	0	3	50.0
Jaigobin et al[8]	Canada	13	5	3	0	0	5	61.5
Witlin et al[15]	United States	5*	1	0	0	0	4	20.0
Jeng et al[4]	Taiwan	22	5	3	0	0	14	36.4
Liang et al[1]	Taiwan	21	4	2	0	0	15	28.6
Scott et al[7]	United Kingdom	12	1	3	0	0	8	33.3
Present series	Japan	97	25	16	10	3	43	55.7

Abbreviations: AN, aneurysm; AVM, arteriovenous malformation; CVDs, cerebrovascular diseases; MMD, moyamoya disease.
*Confined to postpartum stroke.

based epidemiologic study in Sweden conducted by retrospective *International Classification of Diseases, Ninth Revision,* code analysis revealed its incidence to be 6.2 (2.4 for subarachnoid hemorrhage and 3.8 for intracerebral hemorrhage) per 100,000 deliveries.[10] A more recent survey in the United States also based on the *International Classification of Diseases, Ninth Revision,* codes reported the incidence of intracerebral hemorrhage to be 6.1 per 100,000 deliveries.[11] In the study in Taiwan, on the other hand, much higher incidence has been reported (31.4 per 100,000 deliveries for all the intracranial hemorrhage).[1]

Causes of the hemorrhage emphasized in the previous studies have been rather different between one and another. In the earlier mentioned survey in the United States, various risk factors including pre-eclampsia/eclampsia, hypertension, and coagulopathy were pointed out and emphasized,[11] but the pre-existing CVDs were not analyzed in detail. A study from France particularly emphasized eclampsia that accounted for 44% of intracerebral hemorrhage although rupture of vascular lesions was found in 37%.[12] Several studies have described CVDs as the cause of hemorrhage, with the detection rate ranging from 21.4% to 61.5% (Table 3), but CVDs were not analyzed deeply, presumably because of the scarcity of such cases in these studies.[1,4,5,7,8,12-15] To the authors' knowledge, the present study of 97 cases is the first to undertake detailed analysis of baseline CVDs in pregnancy-associated stroke.

This study has revealed 2 important findings: first, hemorrhagic stroke conceals baseline CVDs at high frequency, especially before the 32nd week of gestation, and most had not been diagnosed until the bleeding had occurred. It can also be said that CVD-unrelated hemorrhages caused by obstetric complication or unknown etiology occur significantly later than those related to CVDs. The cause of this phenomenon has not been proven, but it is likely that the remarkable physiological changes occurring in late gestation are related to the increase in CVD-unrelated hemorrhage. As to the absolute CVD detection rate, the authors must clearly acknowledge the possibility of inclusion bias: this being a survey of neurosurgical institutes, it is possible that hemorrhagic cases diagnosed as having CVDs in the previous hospital could have been transferred selectively. An examination of the patient transfer state, however, revealed that 55.0% of the pregnant patients with intracranial hemorrhage were directly admitted in the surveyed institutes and that 36.7% had been transferred from the obstetric institution immediately after the diagnosis of hemorrhage without advanced examination of cerebral vascular lesions. This indicates that a total of 91.7% of our cases were free from this bias. Another highly possible bias is that patients with mild hemorrhage were treated by obstetricians or neurologists without a neurosurgeon being consulted and were thus excluded from the present study. Although there has been no evidence that severe hemorrhages are likely to be accompanied with CVDs and mild ones are not, the authors must admit the limitation of the present study with regard to this point. Accordingly, it might be proper to discuss the significant difference in CVD detection rate between the period before and the period after the 32nd week, rather than to argue the absolute value itself. At any rate, it is essential that patients presenting with intracranial hemorrhage during pregnancy be carefully examined for underlying CVDs.

The second novel finding is that AVMs are the predominant bleeding source, being 1.8 times more frequent than cerebral aneurysms during pregnancy. In the general population, AVM rupture is approximately one tenth as frequent as aneurysmal rupture[16,17]; even when confined to young adults, it is still one third as frequent as bleeding from an aneurysm.[18] These findings strongly suggest that physiological changes during pregnancy have a significant impact on the vasculature of AVMs, and ruptures during pregnancy are by no means coincidental. A review of the literature by neurosurgeons once

counted the number of past cases of pregnancy-related hemorrhage from aneurysms and AVMs and described the predominance of aneurysms compared with AVMs (77% versus 23%, respectively),[19] but these data were compiled from different countries and times and included many old case reports before the CT era. Recently, several studies showed the predominance of vascular malformations as shown in Table 2.[1,4,5,8] The small number of cases, however, precluded a robust conclusion about their prevalence. The present survey has clearly disclosed the predominance of AVMs at least in the Japanese population. Because no study proves a higher prevalence of AVMs in Asians than in Caucasians, the authors believe that this predominance is also applicable to Western populations.

All the aneurysms in the present series were emergently clipped or embolized except for 1 case found to be dead on arrival. This strategy apparently follows the recent recommendation that ruptured aneurysms should be managed in the same way as in the nonpregnant population.[19-21] Management of ruptured AVMs during pregnancy, on the other hand, has not yet been discussed in depth. Unlike cerebral aneurysms, AVMs exhibit a wide diversity in their amenability to surgical resection, from small resectable lesions in a noneloquent cortex to huge, deep-seated ones that cannot be removed.[17,22] Consequently, various surgical approaches were applied in the present study, including emergent nidus resection, ventricular drainage, and hematoma removal leaving the nidus unresected. The authors believe that ruptured AVMs should also be managed in the same manner as they are in the nonpregnant population, even during gestation. The mode and timing of surgery should be determined according to the size and location of the nidus, anatomical pattern of drainage, and volume of the intracerebral hematoma.[17,22]

This survey detected 10 hemorrhages caused by moyamoya disease, which accounted for 10.3% of all cases. Recently, pregnancy-associated stroke in moyamoya disease was closely studied in Japan, and the significance of both ischemia and hemorrhage has been emphasized.[23] The authors believe that the findings regarding moyamoya disease are applicable at least to other Asian countries.

A poor prognosis was identified in 36.1% of all the cases, with mortality reaching 10.3% despite aggressive treatment. This raises the question of whether it is possible to avoid these tragedies. Pre-existing CVDs, as described earlier, play a significant role in pregnancy-associated hemorrhagic stroke, and most remain undiagnosed until stroke onset. Certainly, nonpreventable strokes can occur in the absence of CVDs. Some obstetric complications might also be unavoidable. Clearly, however, one key to prevent a tragic hemorrhage is to detect the underlying CVDs before gestation. A routine brain checkup with MR angiography before pregnancy might reveal these lesions, but implementing such a strategy is not realistic from the viewpoints of medical economics, social and ethical issues surrounding marriage, and morbidity resulting from therapeutic intervention for CVDs that have remained asymptomatic. The familial occurrence of cerebral aneurysms, however, is well recognized, although most AVMs are sporadic.[24,25] The incidence of familial intracranial aneurysms (at least 2 affected first-degree relatives in the same family) among the patients of subarachnoid hemorrhage is 6%-10%,[26-28] and the relative risk for cerebral aneurysms among first-degree relatives in familial intracranial aneurysms families has been reported to be 4.2.[24] Moyamoya disease is also known to have genetic components,[29] and a lot of highly aggregated families with moyamoya disease has been reported.[30] Therefore, it should not be unreasonable to consider a medical checkup with brain MR angiography, at least for women anticipating pregnancy who have dense familial history. Although much discussion is needed, a poor maternal prognosis demands that we continue to address ways to prevent tragic pregnancy-associated strokes.

Conclusions

A nationwide survey revealed that underlying CVDs play an important role in hemorrhagic stroke associated with pregnancy, among which AVM is the predominant bleeding source. Careful examination for vascular lesions is, therefore, essential when dealing with intracranial hemorrhage, especially before the 32nd week of gestation. As maternal prognosis after hemorrhagic stroke has been proved to be poor, a greater effort should be made to prevent tragic pregnancy-associated stroke.

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Annual report of Subcommittee for Examination of Causes of Maternal Death and their Prevention in Perinatology Committee, Japan Society of Obstetrics and Gynecology, 2013

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Introduction

Hemorrhage in the third stage of labor is the most frequent cause of maternal death. A national survey conducted by the subcommittee last year revealed the following bleeding-related factors during the third stage of labor: (i) atonic bleeding; (ii) abnormal placental adherence; (iii) abnormal placental adherence plus atonic bleeding; and (iv) placental abruption. In short, atonic bleeding is the most important factor associated with massive bleeding during the third stage of labor. In addition to this, the following two studies have been conducted this year:

Study 1

A secondary investigation to clarify the pathology of frequently occurring atonic bleeding, involving the same patients as those studied last year.

Study 2

To examine the relationship between the type of amniotic fluid embolism and autopsy findings, in order to clarify the pathology of amniotic fluid embolism and improve the survival rate.

Discussion

In study 1, the results demonstrated that the fibrinogen level decreases earlier than the platelet count and antithrombin III (AT III) activity when atonic bleeding occurs; however, the fibrinogen level was measured immediately after occurrence in only 33% of all patients. Considering that the fibrinogen level was not correlated with the platelet count or AT III activity, it may be important to measure fibrinogen levels in early stages, in order to determine the pathological condition and severity of atonic bleeding. While myometrial fatigue due to prolonged labor and weak pains generally regarded as the main cause of atonic bleeding, in this study, its occurrence was not associated with prolonged labor, weak pains or the use uterotonic agents. On the other hand, with an increase in the volume of bleeding and obstetrical disseminated intravascular coagulation (DIC) scores, packed red blood cells and fresh frozen plasma (FFP) were administrated. As the fibrinogen level decreases early in atonic bleeding, the early administration of FFP may be important as an initial approach to treat the disease.

In study 2, amniotic fluid embolism was classified into two types: that involving cardiopulmonary collapse; and that following DIC. Pathologically, the former type is conventional, in which fetal and amniotic fluid

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components are observed in pulmonary blood vessels. The pathological characteristics of the latter type include uterine atony, and the presence of fetal and amniotic fluid components in uterine blood vessels. In this type, fetal and amniotic fluid components are occasionally absent in the lungs. Among cases of clinical amniotic fluid embolism without fetal and amniotic fluid components in the lungs (or pulmonary examination findings are unavailable in life-saving settings), those involving uterine atony in the presence of fetal and amniotic fluid components in uterine blood vessels may be called uterus-type amniotic fluid embolism.

Disclosure

The authors have no conflict of interest to declare.

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