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第2特集

4 経頭蓋直流電気刺激法と脳腫瘍手術

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経頭蓋直流電気刺激法とは

1. 脳の可塑性

経頭蓋直流電気刺激法とは、微弱な1～5mAの直流電流を頭皮上に貼った電極から流すことで、脳の可塑性を誘導して治療効果を高めようとする方法です。ヒトの脳は病気になると、状況に応じて臨機応変に、周辺の正常な脳組織が失われた機能を取り戻そうとする性質があります。これを脳の可塑性（かそ）といいます。

2. 治療方法

治療は簡単かつ安全に行えます。治療する部位に5×5cmまたは5×7cmの大きさの電極を貼ります（**図1、2**）。そこへ刺激装置（スティムレーター）から送り出される、微弱な1mAから最大5mA程度の直流電流を流して、頭皮から頭蓋内へ通電します。直下の大脳皮質の神経活動が変化し、これを治療に応用します。陽極（**図1c**）で刺激すると電極直下の神経活動が興奮します。反対に陰極（**図1b**）で刺激すると電極直下の神経活動は抑制されます。

効果は1時間～1時間半程度、継続します。皮膚の切開といった手術は必要ありません。治

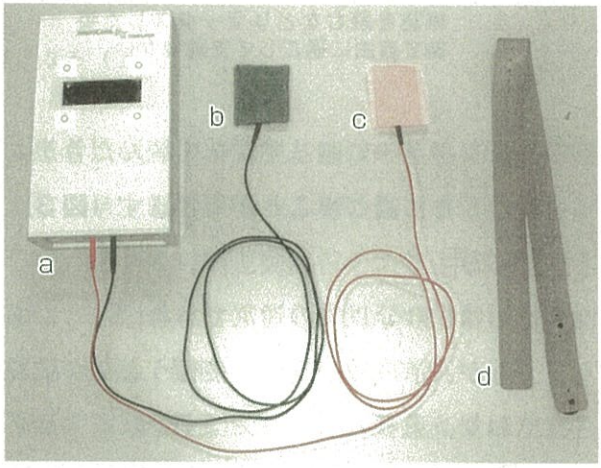

図1 ■ 経頭蓋直流電気刺激法の治療システム一式

a：刺激装置（スティムレーター）、b：陰性電極（5×7cm）、c：陽性電極（5×7cm）、d：電極固定用ゴムバンド。

図2 ■ 刺激の実際

a：右側陽極直下で神経活動の刺激。左側陰極直下では抑制が誘導される。この貼り方では左側からの半球間抑制が解除できる。
b：右側の賦活のみを目的とする場合は刺激部位に陽極を、基準電極（陰極）を反対側前頭部に置く。
c：右側の抑制のみを目的とする場合は刺激部位に陰極を、基準電極（陽極）を反対側前頭部に置く。

図3 ■ 治療中の様子

治療時間は 20 ～ 30 分。治療中は雑誌を読むなどリラックスした姿勢で自由に過ごして支障はない。

療中は、ソファーに座って雑誌を読んだりテレビを見たりして過ごすことができます（**図 3**）。

3. 副作用

副作用は、30 分以内の通電であればとくにありませんが、治療は医師が直接行うことが推奨されており、患者の安全性には十分配慮する必要があります。通電時のぴりぴり感や軽度の頭痛、皮膚の発赤などの報告もありますが、いずれも重篤なものではないようです。

4. 経頭蓋直流電気刺激法の将来性

経頭蓋直流電気刺激法は、現在、保険診療として認可されていません。病院の倫理審査委員会に申請し審議され、許可を得てから行う必要があります。現時点ではあくまで研究用ですが、日本を含めて世界中で臨床研究が活発に行われています。近い将来、脳神経外科におけるさまざまな病気に対する標準治療の一つとなる有効な方法です。

◆対象疾患・病態

1. 対象疾患と作用のメカニズム

対象となる脳の疾患には、脳腫瘍、脳卒中、高次脳機能障害、耳鳴、慢性疼痛およびうつ病などがあります。脳腫瘍や脳卒中の患者で片麻痺をきたしている場合には、病変部位を陽極刺激（神経活動を促進させる）し、健側に陰性刺激（神経活動を抑制する）を行います。脳内に病変があると健側脳が病変側の脳を抑制して、ますます手足が動かなくなる「半球間抑制」という現象が引き起こされることがあります。これに対して病変側を陽極で、健側を陰極で刺激するのは理にかなっています。半球間抑制を解除し、さらに病変部位の活動を促進できるからです。陽極刺激だけあるいは陰極刺激だけでよい場合は、もう一方の電極（基準電極）は反対側前頭部（額）に貼ります。

2. 経頭蓋直流電気刺激法の応用

高次脳機能障害では、2 つ 3 つ以上の仕事を並行して行えなくなります。たとえば主婦の場合、煮込み物をしながら、炒め物をつくり、玄関で郵便の受け取りをするなど、普段行っていることができなくなるわけですから、日常生活や仕事で支障をきたします。このような症状に対しては、左側前頭葉の外側部位を陽極刺激すると効果があります。

難治性の耳鳴に対しては、中枢性つまり側頭葉にある聴覚中枢の過活動が原因とする説があり、ここを陰極で刺激して神経活動を抑制することで治療に応用します。脳の帯状回（前頭葉

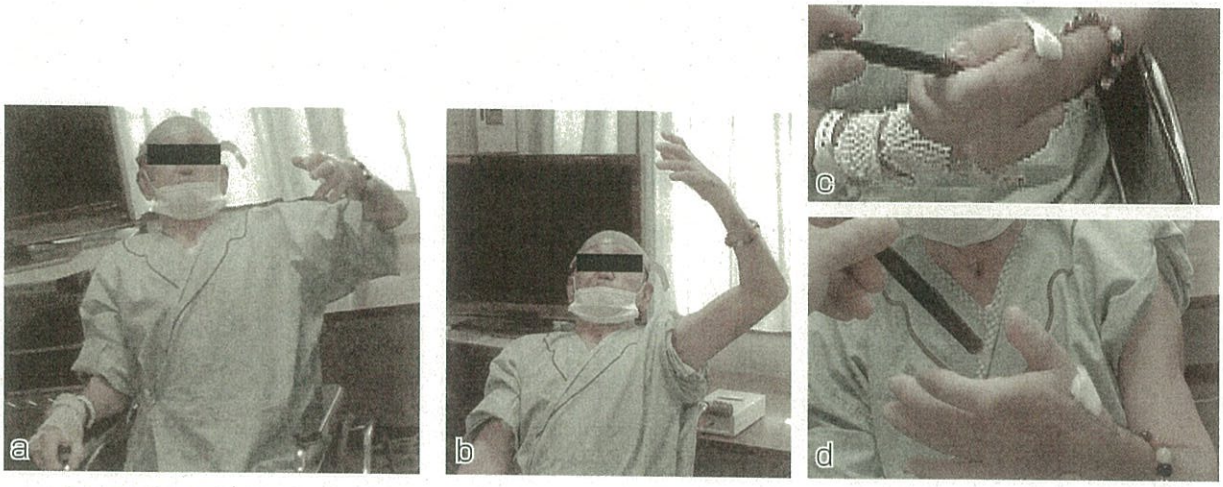

図4 ■ 治療前後の様子

a：治療前、b：治療後の左上肢挙上。
刺激後にはボールペンをつかみ（c）、離すことが可能となる（d）。

の内側部分）で痛みが増幅されて症状を出す慢性疼痛と、薬物が効きにくい難治性うつ病では、中心溝周囲（一次運動野 M1 および一次感覚野 S1 を含む領域）を刺激すると、症状の安定が得られます。この部位を刺激すると多幸感を誘導する内因性（脳が自分でつくる）の麻薬が産生され、症状改善につながるようです。

このようにさまざまな病気に対して経頭蓋直流電気刺激法が応用されていますが、今後さらに症例を増やして、より有効性の高い刺激法の確立や、治療による背景の神経回路網の変化の詳細を明らかにする必要があります。

◆経頭蓋直流電気刺激法を使ったニューロリハビリの実際

ここでは、運動麻痺の改善を目的に、一次運動野へ通電した脳腫瘍患者に対する治療の実際を示します（**図4**）。

患者は脳深部・大脳基底核の腫瘍によって左上肢の挙上制限があり、胸の高さまでしか上がらず、左手の巧緻運動障害があり、物を手で握ることができませんでした。この患者は病変側 M1 に陽極、健側 M1 に陰極を置いて通電しました。1回の経頭蓋直流電気刺激直後にただちに改善が認められています。左上肢は頭部より高く挙上できるようになりました。また治療前にはボールペンをつかめませんでしたが、治療後はボールペンをつかんで離すこともできるようになりました。

機能的な磁気共鳴画像で検査すると、手が動かなかった治療前には一次運動野に血流の上昇はありませんが、通電後には左右の運動野と中心部の補足運動野にも血流の上昇を認めています。経頭蓋直流電気刺激によって、脳の機能的な活性が誘導された証拠です。何回か治療を繰り返すことで可塑性が高まり、症状の改善に結びつきます。

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Full paper

Effect of caffeine contained in a cup of coffee on microvascular function in healthy subjects

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ABSTRACT

Recent epidemiological studies have demonstrated that coffee drinking is associated with reduced mortality of cardiovascular disease. However, its precise mechanisms remain to be clarified. In this study, we examined whether single ingestion of caffeine contained in a cup of coffee improves microvascular function in healthy subjects.

A double-blind, placebo-controlled, crossover study was performed in 27 healthy volunteers. A cup of either caffeinated or decaffeinated coffee was drunk by the subjects, and reactive hyperemia of finger blood flow was assessed by laser Doppler flowmetry. In an interval of more than 2 days, the same experimental protocol was repeated with another coffee in a crossover manner. Caffeinated coffee intake slightly but significantly elevated blood pressure and decreased finger blood flow as compared with decaffeinated coffee intake. There was no significant difference in heart rate between caffeinated and decaffeinated coffee intake. Importantly, caffeinated coffee intake significantly enhanced post-occlusive reactive hyperemia of finger blood flow, an index of microvascular endothelial function, compared with decaffeinated coffee intake.

These results provide the first evidence that caffeine contained in a cup of coffee enhances microvascular function in healthy individuals.

1. Introduction

Coffee is the most widely consumed beverage in the world (1). Coffee contains a variety of pharmacologically active ingredients, and it has long been argued whether coffee drinking is beneficial or harmful for cardiovascular disease (2–4). Recently, a large cohort study, in which more than 400,000 participants were prospectively followed up for 13 years, has demonstrated that coffee consumption is associated with reduced mortality of cardiovascular disease (5). Moreover, a meta-analysis of 23 prospective studies has provided quantitative evidence that coffee intake is inversely related to cardiovascular disease mortality (6). These findings suggest the beneficial cardiovascular actions of coffee. However, its precise mechanisms remain to be elucidated.

The vascular endothelium synthesizes and releases several vasodilating substances, such as prostacyclin, nitric oxide, and endothelium-derived hyperpolarizing factors (EDHF). Evaluation of endothelial function has been shown to provide important prognostic information in patients with cardiovascular disease, as evidenced by the facts that the severity of endothelial dysfunction can predict future cardiovascular events (7, 8) and that improvement of endothelial function by pharmacological interventions reduces the risk of cardiovascular disease. Acute effects of caffeine, a major

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pharmacologically active ingredient of coffee, on human endothelial function of large conduit arteries have been examined in several previous studies by using ultrasound-based measurement of brachial artery diameter during post-occlusive reactive hyperemia. However, the results of those studies are quite inconsistent (9–13). It is generally accepted that flow-dependent dilation of conduit arteries is mediated primarily by nitric oxide (14), while in the microcirculation EDHF rather than nitric oxide have been suggested to play a major role in the reactive hyperemic response (15). Microvessels, but not large arteries, regulate tissue blood blow and systemic blood pressure, and thereby play a key role in the circulatory system. However, no study has ever addressed the effect of caffeine on microvascular function.

Based on the above background, we examined in this study the effect of single ingestion of a cup of caffeinated and decaffeinated coffee on finger microvascular function in healthy subjects by laser Doppler flowmetry.

2. Methods

2.1. Subjects

We recruited twenty-seven healthy subjects (13 men and 14 women; 22–30 years old [mean age, 23.7 ± 2.2]; mean body weight, 58.4 ± 15.1 kg; mean height, 162.9 ± 9.6 cm) in our university, and the subjects who wanted to take part in the study voluntarily were investigated. Subjects taking any medication or smokers were excluded from the study, and the experiments were performed when the subjects were well conditioned. All volunteers were asked to abstain from caffeine-contained beverages at least 12 h before the study. All subjects gave written informed consent, and invasive experiments including blood sampling were approved by the Clinical Trial Ethics Committee of the University of the Ryukyus, according to the declaration of Helsinki and the ethical standard.

2.2. Study design

A double-blind, placebo-controlled, crossover study was performed. All participants were examined on two separate days in a quiet temperature-controlled room. Instant coffee of 2 g with or without caffeine (Taster's Choice™, Nestlé, Vevey, Switzerland) was prepared with 150 ml hot water. Neither sugar nor milk was added. A cup of the caffeinated or decaffeinated coffee was ingested in each subject. Hemodynamic variables and reactive hyperemic response were measured before and every 15 min after coffee intake. In a pilot study, we were not able to continue this experiment more than 75 min because some subjects complained of strong pain due to repeated cuff-compression or a fixed position of the test arm. Thus, we set the experiment time for 75 min. In an interval of more than 2 days, the same experimental protocol was repeated with another coffee in a crossover manner. Blood pressures were measured at the brachial artery using a sphygmomanometer (BP-103i, Nihon Colin, Komaki, Japan). A manchette was placed around the right upper arm, and a mean value of three measurements was used for the statistical analyses. Heart rate was obtained from the sphygmomanometer. The subjects were in a sitting position throughout the experiments.

2.3. Assessment of microvascular function

Finger blood flow was measured by a laser Doppler flowmeter (ALF21, Advance, Tokyo, Japan). A flow-probe (type C) was placed at the tip of the left index finger or thumb. Blood flow was calculated by measuring Doppler shifts derived from moving erythrocytes per photon and the mean photon frequency. As the number of Doppler shifts is proportional to the erythrocyte volume and velocity, blood flow is the product of linearized volume and velocity (16). Post-occlusive reactive hyperemia of finger blood flow was assessed as an index of microvascular endothelial function. A cuff was placed on the left upper arm, and reactive hyperemia of finger blood flow was induced by inflating a cuff for 1 min in order to interrupt arterial blood flow and then deflating it. Peak hyperemic flow was defined as the highest blood flow immediately after cuff deflation. Reactive hyperemia was calculated according to the following equation:

Reactive hyperemia (%) = [(peak hyperemic flow − resting flow)/resting flow] × 100

2.4. Measurement of caffeine and catecholamine levels

Venous blood samples were collected before and 30 min after coffee ingestion in five volunteers. The plasma caffeine levels and caffeine contents in decaffeinated and caffeinated coffee were analyzed by high performance liquid chromatography (HPLC; LC-10AD, Shimadzu, Kyoto, Japan) (17). Plasma catecholamine levels were measured by SRL Inc. (Tokyo, Japan) using the HPLC method.

2.5. Statistical analysis

Statistical analyses were performed by a two-way ANOVA followed by a Bonferoni/Dunn post hoc test. When paired or unpaired data were compared, a paired or unpaired Student's *t*-test, respectively, was applied. The computer software StatView-J 5.0 (SAS Institute Japan Ltd, Tokyo, Japan) was used for the statistical analyses. A value of $P < 0.05$ was considered to be statistically significant. Results are expressed as mean ± SD.

Reproducibility of laser Doppler flowmetry was expressed as within-subject coefficients of variability. In our laboratory, the intra-day variability for finger blood flow was 6.3% (range: 0–27.1%) and that for reactive hyperemia assessed by laser Doppler flowmetry was 21.6% (0–54.2%), and the day-to-day variability for finger blood flow was 26.2% (0–76.1%) and that for reactive hyperemia was 33.7% (0–102%). According to the previous studies, the coefficient of variance < 35% can be deemed acceptable (18).

3. Results

3.1. Caffeine content in decaffeinated and caffeinated coffee and plasma caffeine levels before and after coffee intake

Caffeine content in decaffeinated vs. caffeinated coffee was markedly different (1.37 ± 0.09 vs. 54.5 ± 3.4 mg, respectively) (Fig. 1A). Before coffee intake, plasma caffeine levels were identical between subjects with decaffeinated and caffeinated coffee intake. However, 30 min after coffee intake, plasma caffeine levels were markedly increased in the subjects with caffeinated coffee intake (from 0.75 ± 0.85 to 1.57 ± 1.30 μg/ml, $P < 0.05$), but not in those with decaffeinated coffee intake (from 0.76 ± 0.57 to 0.77 ± 0.60 μg/ml) (Fig. 1B).

3.2. Effects of caffeinated coffee intake on blood pressure and finger blood flow

Before coffee intake, there were no significant differences in baseline hemodynamic variables (i.e., systolic, diastolic, and mean blood pressures, finger blood flow, vascular resistance, or heart rate) in the subjects with decaffeinated and caffeinated coffee intake (Table 1). However, caffeinated coffee intake, but not

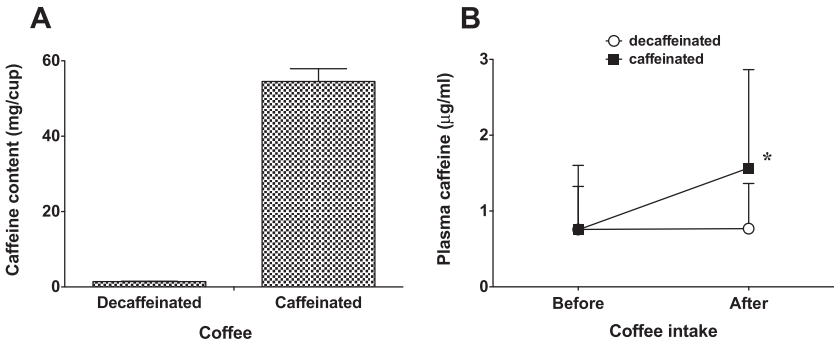

Fig. 1. Caffeine contents in a cup of decaffeinated and caffeinated coffee (A) and plasma caffeine levels before and 30 min after single intake of caffeinated and decaffeinated coffee (B). Data are expressed as mean ± SD. *$P < 0.05$ between before and after coffee intake by a paired *t*-test.

decaffeinated coffee intake, caused slight but significant elevations of systolic, diastolic and mean blood pressures by maximally 2.7, 3.2 and 2.8 mmHg, respectively (each $P < 0.01$, Fig. 2). Furthermore, caffeinated coffee intake significantly reduced finger blood flow (as assessed by laser-Doppler flowmetry, $P < 0.01$, Fig. 3A) and significantly increased vascular resistance of the finger vascular bed when compared with decaffeinated coffee intake ($P < 0.01$, Fig. 3B). On the other hand, there was no significant difference in heart rate in the subjects with decaffeinated and caffeinate coffee intake (Fig. 3C).

3.3. Effects of caffeinated coffee intake on reactive hyperemia of finger blood flow

Before coffee intake, post-occlusive reactive hyperemia of finger blood flow, an index of microvascular endothelial function, were comparable between the subjects with decaffeinated and caffeinated coffee (8.7 ± 4.3 and 10.0 ± 3.4 ml/min/100 g, respectively). However, caffeinated coffee intake significantly enhanced post-occlusive reactive hyperemia of finger blood as compared with decaffeinated coffee intake ($P < 0.01$, Fig. 4).

3.4. Plasma catecholamine levels

Plasma norepinephrine levels did not significantly differ between the subjects with decaffeinated and caffeinated coffee intake at baseline (336 ± 132 vs. 317 ± 165 pg/ml) and at 30 min after the intake (271 ± 95 vs. 272 ± 125 pg/ml). Plasma epinephrine levels also did not significantly alter between the subjects with decaffeinated and caffeinated coffee intake at baseline (35.8 ± 12.5 vs. 33.3 ± 18.5 pg/ml) and at 30 min after the intake (32.0 ± 11.2 vs. 25.8 ± 13.5 pg/ml). The respective plasma catecholamine levels did not significantly change before and after coffee intake.

Table 1
Baseline characteristics in subjects with decaffeinated and caffeinated coffee intake.

Variables	Decaffeinated	Caffeinated	*P* value
Systolic BP (mmHg)	104.9 ± 12.4	106.2 ± 11.2	0.346
Diastolic BP (mmHg)	58.0 ± 8.3	59.1 ± 6.6	0.297
Mean BP (mmHg)	73.6 ± 8.8	74.8 ± 7.6	0.264
Finger blood flow (ml/min/100 g)	23.6 ± 7.7	23.3 ± 7.9	0.916
Vascular resistance (unit)	3.43 ± 1.15	3.67 ± 1.63	0.543
Reactive hyperemia (%)	40.8 ± 25.4	50.3 ± 27.1	0.125
Heart rate (bpm)	74.6 ± 9.4	74.3 ± 8.6	0.815

BP = blood pressure, Vascular resistance = vascular resistance of the finger vascular bed (finger blood flow/mean BP), Reactive hyperemia (%) = 100 × (post-occlusive increase in finger blood flow)/(baseline finger blood flow).

4. Discussion

To the best of our knowledge, this is the first study examining the acute effect of caffeine on endothelial function in the human finger cutaneous microcirculation. The present study demonstrates that an intake of caffeine contained in a cup of coffee may cause a favorable effect on microvascular endothelial function assessed by a noninvasive laser Doppler flowmetry method in Japanese young healthy subjects.

4.1. Pressor effect of caffeine

In the present study, the plasma caffeine concentration after caffeinated coffee intake attained 1.6 μg/ml. This concentration of caffeine has been shown to act as an antagonist of adenosine A_1/A_{2A} receptors (19, 20). As adenosine causes vasodilation in most vascular beds (21), caffeine would induce an increase in vascular resistance. Thus, slight but significant rises in blood pressure observed after caffeinated coffee intake in the present study may, in part, be caused by an increase in basal vascular tone derived from the adenosine antagonism of caffeine, as found by an early study (22). In addition, a direct stimulatory effect of caffeine on myocardial contractility (23) might be involved in a significant increase in blood pressure seen after caffeinated coffee intake.

4.2. Effect of caffeine on microvascular function

The present finding that caffeine ingestion, even at a small dose (54.5 mg = less than 1 mg/kg), improves microvascular endothelial function is consistent with a previous study (24) using venous occlusion plethysmography demonstrating that the acute administration of caffeine at an extremely large dose (300 mg) augments vasodilator responses of forearm vessels to intra-arterial infusion of the endothelium-dependent agonist acetylcholine.

In contrast to our study, however, two previous reports using ultrasound-based measurement of brachial artery diameter during post-occlusive reactive hyperemia demonstrated that caffeinated coffee ingestion impaired endothelial function in healthy volunteers (9, 12). In addition, two other studies showed that acutely administered caffeine had no effect on endothelial function assessed by the brachial artery vasoreactivity measurement (10, 11). Although the reason for conflicting with our data cannot be fully explained at present, it seems plausible that the difference in the type of vessels used for assessing vascular function was mainly involved. Laser Doppler flowmetry employed in the present study measures microvascular function in cutaneous arterioles and capillaries, whereas the ultrasound-based measurement of brachial artery diameter reflects 'macrovascular' function in large conduit

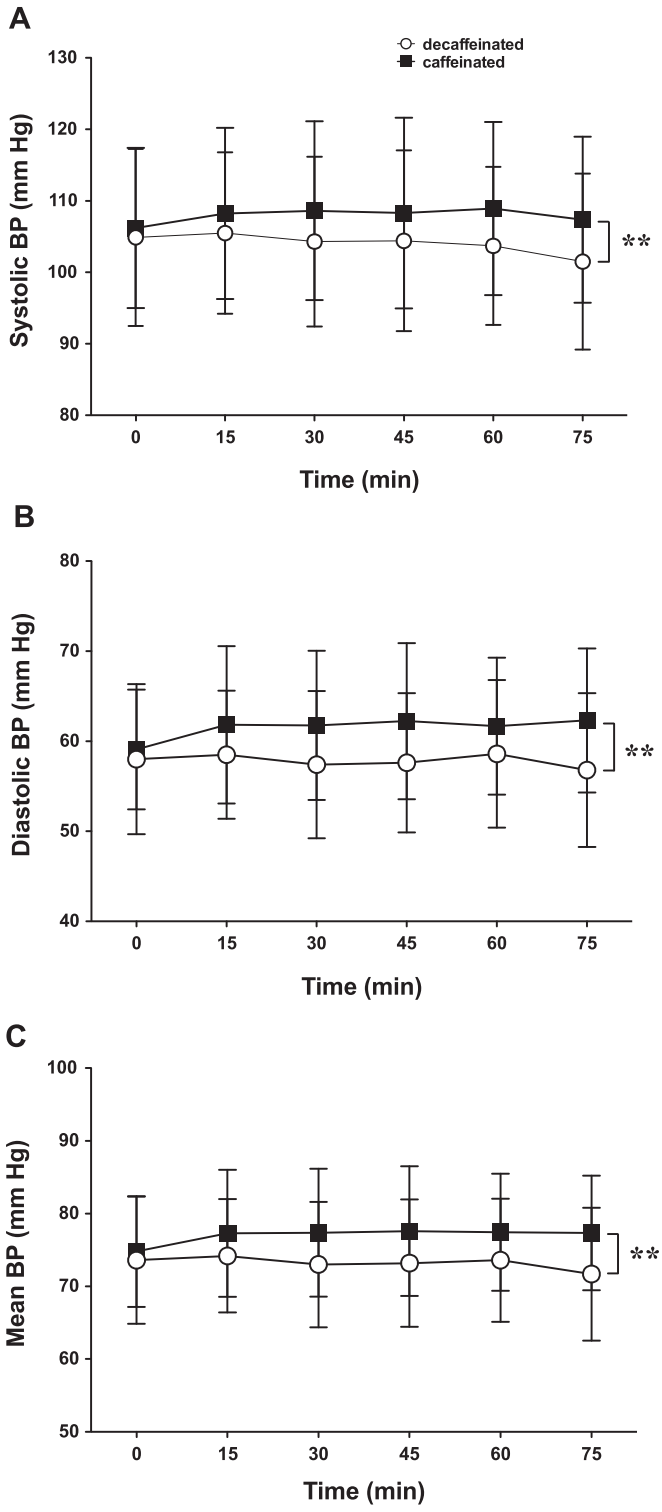

Fig. 2. Effects of caffeinated and decaffeinated coffee intake on systolic (A), diastolic (B) and mean (C) blood pressures (BP). Data are expressed as mean ± SD. $^{**}P < 0.01$ between caffeine (−) and caffeine (+) by ANOVA.

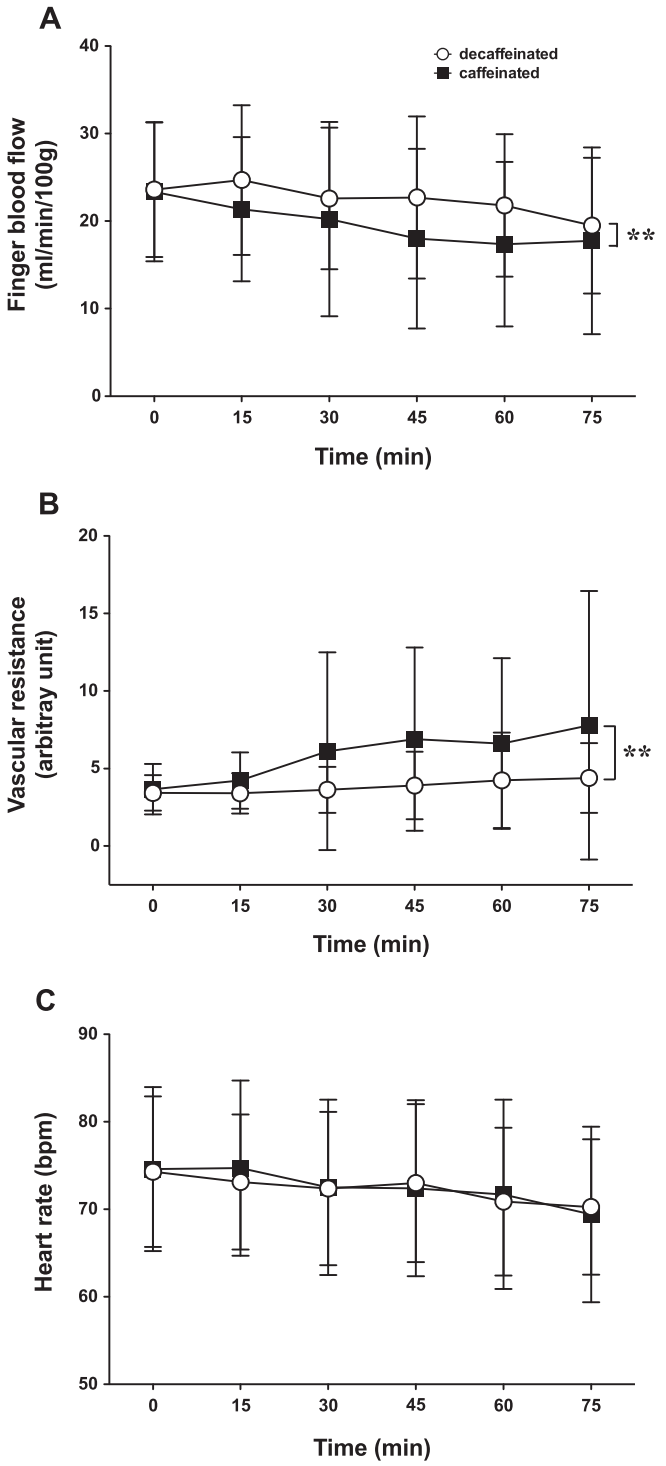

Fig. 3. Effects of caffeinated and decaffeinated coffee intake on finger blood flow (A), vascular resistance of the finger vascular bed (B), and heart rate (C). Data are expressed as mean ± SD. $^{**}P < 0.01$ between caffeine (−) and caffeine (+) by ANOVA.

arteries. Indeed, some previous studies have described that brachial artery responses to reactive hyperemia do not correlate with microvascular function as measured by agonist infusion studies or laser Doppler flowmetry (25, 26). It is generally considered that flow-dependent dilation of conduit arteries is mediated primarily by nitric oxide (14). By contrast, contribution of nitric oxide to post-occlusive reactive hyperemia in microvessels appears minimal (27, 28). Instead, EDHF may have a major role in the reactive hyperemic response in the microcirculation (15). Although the nature and mechanisms of EDHF remain uncertain, EDHF response has been proposed to be divided into two broad categories as follows: the first (classical) EDHF pathway is associated with endothelial cell hyperpolarization due to the opening of endothelial calcium-

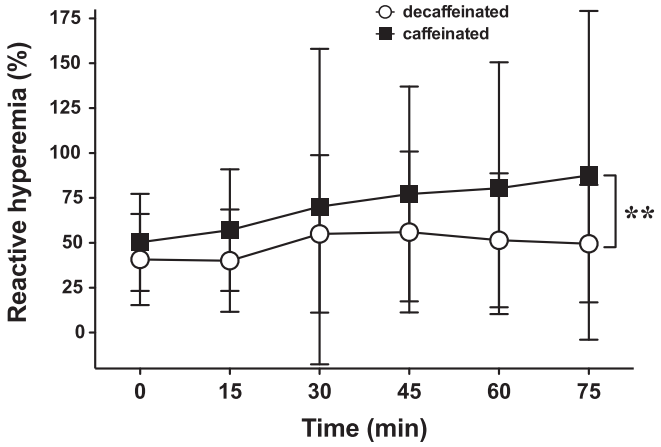

Fig. 4. Effect of caffeinated and decaffeinated coffee intake on post-occlusive reactive hyperemia of finger blood flow. Reactive hyperemia was calculated according to the following equation: reactive hyperemia (%) = [(peak hyperemic flow − resting flow)/resting flow] × 100. Data are expressed as mean ± SD. $^{**}P < 0.01$ between caffeine (−) and caffeine (+) by ANOVA.

activated K^+-channels, and the second EDHF pathway does not require endothelial hyperpolarization but involves the endothelial release of factors that hyperpolarize vascular smooth muscle cells by opening various myocyte K^+-channels such as calcium-activated K^+-channels (29). Experimental studies with animal and human vessels have demonstrated that the activation of vascular smooth muscle Ca^{2+}-activated K^+ channels probably contributes to the EDHF component of reactive hyperemia in microvessels (30, 31). Thus, microvascular endothelial function assessed by laser Doppler flowmetry may reflect the bioavailability of endothelium-dependent hyperpolarization via the activation of Ca^{2+}-activated K^+ channels in the endothelium and/or vascular smooth muscles.

4.3. Possible mechanisms involved in the beneficial effect of caffeine on microvascular function

In addition to the action on adenosine receptors, caffeine has been known to have a variety of pharmacological properties, including inhibition of phosphodiesterase (32), and calcium release from intracellular calcium stores via ryanodine-sensitive calcium channels (33). Interestingly, several electrophysiological experiments have displayed that caffeine at concentrations ranging from 10^{-6} to 10^{-3} M evokes calcium-dependent hyperpolarization in endothelial cells and vascular smooth muscle cells as a result of increased outward K^+ current (34–36). These data suggest that caffeine-induced release of calcium from intracellular calcium stores elicits the activation of calcium-activated K^+-channels in these cells. Considering that EDHF, unlike nitric oxide, has a major role in microvascular reactive hyperemia, it is possible that caffeine has the potential to augment the reactive hyperemic response of microvessels through amplifying hyperpolarization caused by EDHF. This may explain a favorable effect of caffeine on microvascular endothelial function in the present study, because the plasma concentration of caffeine was estimated to be nearly 10^{-5} M (Fig. 1B). It is intriguing that previous experiments in rats have shown that treatment with blockers of calcium-activated K^+-channels dose not affect baseline blood pressure or vascular conductance but attenuates vasodilator responses of resistance vessels produced by endothelium-dependent vasodilators such as acetylcholine (37, 38). These findings indicate that calcium-activated K^+-channels contribute little to the regulation of basal blood pressure but participate in responses to endothelial stimulation, and may be related to the present results that caffeine intake produced enhancement of microvascular endothelial function in spite of the occurrence of a slight increase in baseline blood pressure.

Several clinical studies (13, 39–41) have shown that caffeine exerts acute beneficial metabolic effects such as increased concentrations of adiponectin, a marker of anti-inflammatory and insulin-sensitizing effects (42). In addition, a cross-sectional study has reported that coffee consumption is inversely associated with a plasma marker of inflammation (C-reactive protein) and that of endothelial dysfunction (E-selectin) (43). Thus, these preferable properties of caffeine, besides the effect on endothelial function, may partly account for the beneficial cardiovascular effect of long-term coffee consumption.

4.4. Study limitations

Our study has some potential limitations to be considered. First, the number of subjects examined in this study may have been so small as to provide conclusive proof, although statistically significant effects were found. Second, the long-term effects of caffeine ingestion on endothelial function remain unknown. Third, we did not ask female subjects about the menstrual cycle, and it is thus unknown to what extent its phases affected the finger blood flow response. Finally, assessment of microvascular function was performed solely in Japanese healthy young volunteers. We have not yet elucidated whether or not caffeinated coffee intake ameliorates microvascular endothelial function not only in healthy subjects but also in patients with cardiovascular disease. These issues remain to be examined in future studies.

5. Conclusion

Our double-blind, placebo-controlled, crossover study has demonstrated, for the first time, that caffeine at the amount contained in a cup of coffee may cause improvement of microvascular endothelial function in healthy subjects.

Conflict of interest

None.

Acknowledgments

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Progression of cerebellar chronic encapsulated expanding hematoma during late pregnancy after gamma knife radiosurgery for arteriovenous malformation

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Abstract

Background: The etiology and appropriate management strategy of chronic encapsulated expanding hematoma during pregnancy after gamma knife radiosurgery for arteriovenous malformation (AVM) remain unclear.

Case Description: A 34-year-old female developed chronic encapsulated expanding hematoma during late pregnancy, after angiographic disappearance of cerebellar AVM following two courses of gamma knife radiosurgery. The present case implicates pregnancy as a potential promoter of growth and enlargement of chronic encapsulated expanding hematoma, which may become life-threatening and require surgical intervention.

Conclusion: Immediate surgical management after delivery may be associated with a favorable outcome, so close follow-up management and patient education are very important in women planning pregnancy.

Key Words: Arteriovenous malformation, gamma knife, pregnancy, radiosurgery

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INTRODUCTION

Gamma knife radiosurgery is an effective treatment for cerebral arteriovenous malformation (AVM) resulting in angiographic disappearance in more than 80-90% of cases. Actual rates of obliteration of cerebellar AVMs, with median target volume of 3.85 cm^3 and median marginal dose of 21 Gy, were 53% at 3 years and 76% at 5 and 10 years.[1] However, relatively rare complications such as cyst formation and chronic encapsulated expanding hematoma may develop more than 5 years after gamma knife radiosurgery even if angiographic disappearance has been achieved.[4,10,15,16,19] Furthermore, little is known about the mechanisms and appropriate management of chronic encapsulated expanding hematoma during pregnancy. We present a case of cerebellar chronic encapsulated expanding hematoma encountered during late pregnancy, 4 years after angiographic disappearance of AVM nidus following two courses of gamma knife radiosurgery, with a cumulative dose of 44 Gy to the margin at the 50-60% isodose line, carried out at an interval of 4 years.

CASE REPORT

A 20-year-old female presented with sudden onset of severe headache associated with nausea followed by disturbance of consciousness, and was admitted to another hospital. The diagnosis of cerebellar and subarachnoid hemorrhage from AVM supplied by the

posterior inferior cerebellar artery (PICA) was based on the findings of computed tomography (CT) [Figure 1a] and cerebral angiography. Emergency evacuation of the hematoma was performed via a midline suboccipital approach. Four months after surgery, vertebral angiography demonstrated left cerebellar hemispheric AVM supplied by the PICA [Figure 1b]. Fourteen months after the initial hemorrhage, gamma knife radiosurgery was performed to treat the AVM nidus with a volume of 0.487 cm^3 at another institution using a Leksell Gamma Knife model B unit (Elekta AB). The procedure was planned using GammaPlan software based on stereotactic digital subtraction angiography and magnetic resonance (MR) imaging. A prescribed dose of 20 Gy was delivered to the lesion margin at the 50% isodose line. Three years after the first radiosurgery, vertebral angiography showed a small residual nidus in the left cerebellar hemisphere [Figure 1c]. The patient underwent repeat radiosurgery at the previous institution using a Leksell Gamma Knife model C unit (Elekta AB) 4 years after initial radiosurgery. The target volume of the nidus was 1.5 cm^3, a larger volume than that at the initial radiosurgery, and was intended to improve the treatment efficacy. The procedure was planned using GammaPlan software and a prescribed dose of 24 Gy was delivered to the lesion margin at the 60% isodose line. Vertebral angiography obtained at 5 years after the second radiosurgery revealed complete disappearance of the AVM [Figure 1d]. However, T2-weighted MR imaging and postcontrast T1-weighted MR imaging obtained at 7 years after the second radiosurgery revealed an enhanced lesion adjacent to the cyst formation in the left cerebellar hemisphere [Figure 2a, b]. The patient was lost to follow up during the 18 months after the last examination. The patient subsequently presented with headache and nausea, which had persisted over 3 weeks, at age 34 years in the 32nd week of pregnancy, and was referred to our institution 9 years after the second radiosurgery.

The patient had headache and nausea, but no other neurological deficits were identified except for House–Brackmann grade 3 facial palsy persisting since her childhood. Other medical history was unremarkable. On admission, CT demonstrated an irregularly shaped, heterogeneous high density hematoma with perifocal edema in the vermis extending to the left cerebellar hemisphere [Figure 2c]. Her infant was delivered by cesarean section immediately after admission and osmotic therapy was started. Despite conservative management, disturbance of consciousness developed and deteriorated due to the extensive perifocal edema and hydrocephalus. Three-dimensional CT angiography revealed no vascular abnormality around the lesion.

Midline suboccipital craniotomy was performed and cerebrospinal fluid was released from the ventricular drainage. A very firm, reddish angiomatous nodular granuloma with adjacent cyst was visualized in the cerebellar hemisphere. Indocyanine green videoangiography confirmed the absence of abnormal vasculature around the lesion. The lesion contained angiomatous capsule and firm organized hematoma. Gross total resection was achieved without injury to the surrounding structures. No AVM nidus was observed during surgery. Her symptom was completely resolved

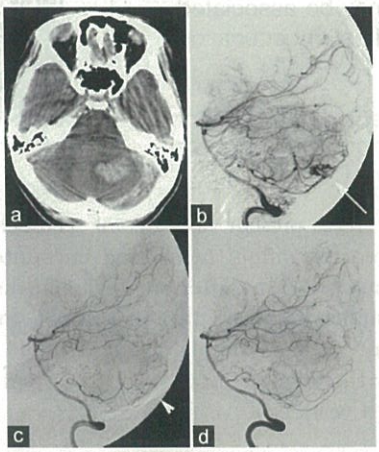

Figure 1: (a) CT scan at initial onset demonstrating left cerebellar hemorrhage with subarachnoid hemorrhage. (b) Left vertebral angiogram before first gamma knife radiosurgery showing a left cerebellar hemispheric AVM supplied by posterior inferior cerebellar artery (*arrow*). (c) Left vertebral angiogram at 3 years after first radiosurgery revealing residual nidus in the left cerebellar hemisphere (*arrowhead*). (d) Left vertebral angiogram obtained at 5 years after the second radiosurgery revealing no residual AVM nidus

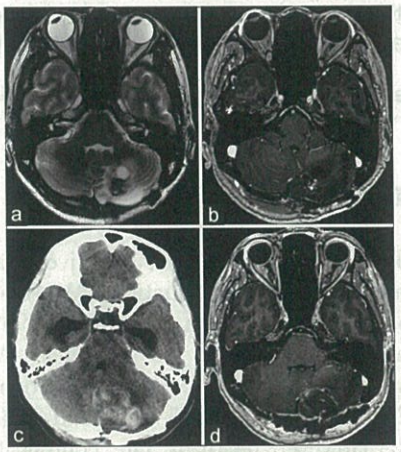

Figure 2: Axial T2-weighted MR image (a) and postcontrast T1-weighted MR image (b) demonstrating appearance of the enhanced lesion adjacent to the cyst formation in the left cerebellar hemisphere at 7 years after second radiosurgery. (c) CT scan showing an irregularly shaped, mixed density lesion with extensive edema in the left cerebellar hemisphere. (d) Postoperative gadolinium-enhanced T1-weighted MR image demonstrating total removal of the lesion

immediately after surgery and the postoperative course was uneventful. Postoperative MR imaging revealed total resection of the hematoma with the adjacent cyst [Figure 2d]. Postoperative angiography confirmed disappearance of the AVM. Her baby's growth and development was also normal.

Histological examination of the lesion obtained during surgery demonstrated encapsulated hematoma consisting of a dense collagenous outer layer and a granulated, newly vascularized, angiomatous inner layer with extensive multinodular hemorrhage at various stages of organization [Figure 3a]. Hemosiderin deposits and coagulation necrosis were also observed [Figure 3b]. The microvasculature in the inner layer demonstrated inflammatory infiltration in the vascular walls and thickening of the vessel walls with hyaline degeneration, which are characteristic findings of vasculitis [Figure 3c]. Immunohistochemical examination demonstrated strong staining for CD34 in the microvasculature [Figure 3d].

DISCUSSION

Chronic encapsulated expanding hematoma after gamma knife radiosurgery

Chronic encapsulated expanding hematoma is a rare but very important late onset complication after gamma knife radiosurgery for AVMs, and may develop even if angiographic disappearance has been achieved. Surgical treatment may be required due to progression in some cases.[10,15,19] Chronic encapsulated expanding hematoma is often accompanied by cyst formation, which tends to occur in patients followed up for longer than 5 years after gamma knife radiosurgery.[16] Larger nidus volume and higher radiation dose may be risk factors for delayed cyst formation,[4] but cyst formation may still occur despite a relatively small nidus and low prescribed margin dose.[19] Total obliteration can be achieved after repeat stereotactic radiosurgery (SRS) for incomplete obliteration after initial SRS.[8,9,13,23] Delayed cyst formation occurred in 4.6% of cases at a median of 108 months after repeat SRS. In the present case, chronic encapsulated expanding hematoma occurred 9 years after the second radiosurgery for the relatively small residual nidus. The cumulative radiation dose was 44 Gy to the lesion margin, which was presumably high enough to induce the hematoma.

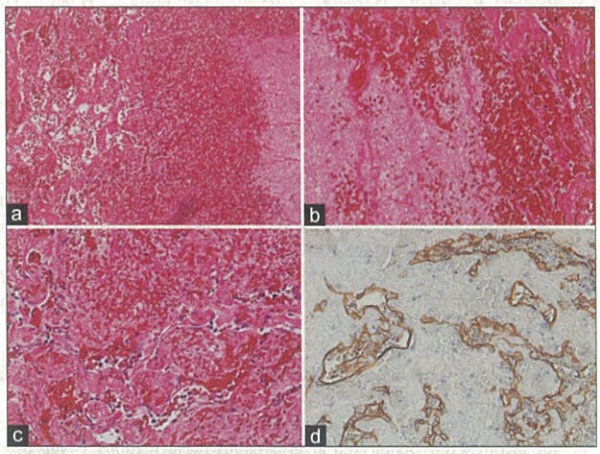

Figure 3: (a) Photomicrographs of the chronic encapsulated expanding hematoma demonstrating angiomatous abnormal vessels, multifocal hemorrhage, and coagulation necrosis. HE, original magnification ×100. (b) Areas of coagulation necrosis and extensive hemorrhage. HE, original magnification ×200. (c) Angiomatous region showing thickening of the vessel walls with hyaline degeneration and inflammatory infiltration. HE, original magnification ×200. (d) Immunohistochemical examination demonstrating strong staining for CD34 in the microvasculature. Original magnification ×200

Chronic encapsulated expanding hematoma during pregnancy

The present case of cerebellar chronic encapsulated expanding hematoma occurred during pregnancy, 9 years after the second radiosurgery. Such occurrence of chronic encapsulated expanding hematoma during pregnancy has not been reported previously, and the etiology and appropriate management strategies remain unclear. Several studies have demonstrated rapid enlargement of intracranial meningiomas during pregnancy.[11,14,22] The rate of presentation increased in the second and third trimesters. Several mechanisms, such as increased blood volume, vascular engorgement, increase in tumor-associated vascularity, increase in intracellular fluid, and increased edema, may explain both the rapid increase in tumor size during pregnancy as well as the frequent partial regression postpartum.[11,12,14,22] Recent studies showed that pregnancy and the puerperium are associated with increased risks of hemorrhage and aggressive behavior in cavernous malformations and other vascular lesions.[3,17] In the present case, the chronic encapsulated expanding hematoma became symptomatic in the third trimester, suggesting relatively rapid progression during pregnancy because this period was only 18 months after the last follow-up examination.

Recent experimental studies have revealed that representative histological changes in smaller arterioles or the microvasculature after irradiation are likely to be caused by microvasculitis, which consists of hyaline degeneration, fibrinoid necrosis, lymphocytic infiltration, and adventitial fibrosis.[2,6,7,18,21] Histological examination of the present case revealed extensive multifocal hemorrhage with multi-stage organization from abnormal angiomatous vessels with hyaline degeneration adjacent to coagulation necrosis. These findings are compatible with those of the experimental studies. On the basis of these findings, we suggest that repeated hemorrhage from the abnormal fragile

vasculature with subsequent multi-stage organization in the lesion occurred during pregnancy due to increased blood volume and vascular engorgement, and this may have caused the rapid enlargement of the hematoma and increased perifocal edema resulting in the progressive deterioration of neurological symptoms during late pregnancy.

The optimum timing for neurosurgical intervention in pregnant patients remains to be elucidated. The indications for surgery and delivery must be determined in relation to the severity of the neurological symptoms in the mother, the aggressiveness of the lesion, and the gestational period.[12] The general recommendation is that neurosurgical intervention should be avoided in the late second and third trimester, because of the high risk of intracranial hemorrhage associated with increased maternal intravascular volume. However, cesarean delivery under general anesthesia with subsequent neurological decompression should be considered for patients with risk of cerebellar herniation.[5,20] Chronic encapsulated expanding hematoma in the cerebellum may cause severe clinical problems and is potentially life-threatening because of the proximity to the brainstem and fourth ventricle. The urgency of such condition increases the likelihood of surgical intervention during pregnancy. Most obstetricians and pediatricians would consider that the delivery should be delayed to 32 weeks of gestation to ensure fetal maturity and survival. In the present case, the patient only complained of headache and was relatively stable on admission, so that cesarean section could be performed under general anesthesia immediately after admission, because the gestational age was 32 weeks and the condition of her infant was stable. After delivery, her neurological status rapidly deteriorated due to increased perifocal edema and development of hydrocephalus, so that midline suboccipital craniotomy was performed. Her neurological deficits were immediately resolved after surgery.

The present case implicates pregnancy as a potential promoter of growth and enlargement of chronic encapsulated expanding hematoma, which may become life-threatening and require surgical intervention. Accurate diagnosis and immediate surgical management after delivery are likely to result in favorable outcome. We suggest that cesarean section followed by craniotomy is indicated for patients with chronic encapsulated expanding hematoma who are neurologically unstable with conservative therapy in late pregnancy.

CONCLUSION

The present case shows that chronic encapsulated expanding hematoma after gamma knife radiosurgery may develop and increase the risk of hemorrhage, with more aggressive behavior during late pregnancy. Craniotomy and total removal of the lesion after delivery by cesarean section under general anesthesia resulted in good outcome. However, the patient should be warned of the risk of this life-threatening complication prior to attempts at becoming pregnant. Therefore, follow-up examinations should be regularly scheduled for young women of child bearing age after gamma knife radiosurgery for AVMs, despite the confirmation of angiographic disappearance of AVM nidus, because of the difficulty in predicting rapid progression of the chronic encapsulated expanding hematoma during pregnancy.

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