ELSEVIER

Aneurysm

TREATMENT OF VERTEBRAL ARTERY ANEURYSMS WITH POSTERIOR INFERIOR CEREBELLAR ARTERY-POSTERIOR INFERIOR CEREBELLAR ARTERY ANASTOMOSIS COMBINED WITH PARENT ARTERY OCCLUSION

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Kakino S, Ogasawara K, Kubo Y, Otawara Y, Tomizuka N, Suzuki M, Ogawa A. Treatment of vertebral artery aneurysms with posterior inferior cerebellar artery-posterior inferior cerebellar artery anastomosis combined with parent artery occlusion. Surg Neurol 2004;61:185–9.

BACKGROUND
In patients with aneurysms that involve the origin of the posterior inferior cerebellar artery (PICA) and require occlusion of the vertebral artery (VA), revascularization of the PICA is commonly performed. We present six patients with dissecting VA aneurysms who underwent PICA-PICA anastomosis combined with parent artery occlusion.

METHODS
After a lower lateral suboccipital craniectomy and partial resection of the jugular tubercle, anastomoses were performed in a side-to-side fashion at the posterior medullary segment of the PICA. The VA was subsequently occluded by clipping proximal and distal to the aneurysm, and the PICA was occluded by clipping distal to the aneurysm.

RESULTS
Postoperative cerebral angiography demonstrated patency of the anastomosis and regression of the aneurysm in five of six patients. The remaining patient experienced hemorrhage from contralateral VA dissection and subsequently died. One patient experienced myopathy of the lower extremities secondary to intraoperative fixed board compression and developed permanent lower extremity muscular weakness. The remaining four cases experienced no new neurologic deficits.

CONCLUSION
PICA-PICA anastomosis is a useful procedure for reconstruction of the PICA when parent vessel occlusion or trapping is necessary to exclude a VA aneurysm involving the origin of the PICA.

KEY WORDS
Cerebral revascularization, posterior inferior cerebellar artery (PICA), PICA-PICA anastomosis, vertebral artery aneurysm.

The treatment of choice for vertebral artery (VA) aneurysms consists of surgical aneurysmal neck clipping. However, large or dissecting aneurysms are not amenable to direct clipping, and concomitant parent vessel occlusion or trapping may be necessary to exclude the lesion from the systemic circulation. Dissecting VA aneurysms occasionally involves the origin of posterior inferior cerebellar artery (PICA). If there is a high probability of PICA blood flow disturbance following surgical treatment for local aneurysm, PICA reconstruction should be considered to prevent lateral medullary syndrome [1,6,8,12,20–22]. Various anastomotic strategies have been employed, including occipital artery (OA)-PICA anastomosis [2,3,5,13,17,18,22], vertebral artery (VA)-PICA anastomosis using a superficial temporal artery (STA) or radial artery (RA) graft (VA-STA/RA-PICA anastomosis) [4,9,10], transposition of the PICA into the VA (VA-PICA transposition) [7]

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and side-to-side anastomosis between the bilateral PICAs (PICA-PICA anastomosis) [14,19]. We describe 6 patients who underwent PICA-PICA anastomosis combined with parent artery occlusion for dissecting VA aneurysm.

PATIENT POPULATION

Between January 1995 and September 2002, 6 patients (4 men, 2 women; mean age 49 ± 4.5 years, range 42–55 years) underwent PICA-PICA anastomosis at our institution. All patients presented with subarachnoid hemorrhage (SAH); 1 case of SAH was classified as Grade I, 1 was Grade Ia, 3 were Grade II, and 1 was Grade III according to the Hunt and Kosnik Scale [11]. The interval between SAH and treatment varied from 2 days to 28 months. Cerebral angiography with arterial catheterization demonstrated dissecting VA aneurysm involving the origin of PICA in all patients. Follow-up periods ranged from 4 days to 31 months (mean 10 months) after surgery. Demographic and clinical presentation data are summarized in Table 1. A detailed report of the second and fourth patient has been published previously [16].

SURGICAL PROCEDURE

Patients were placed in the prone position, with the head flexed at the neck and tilted approximately 20 degrees toward the contralateral shoulder. A paramedian straight incision was made, and a lower lateral suboccipital craniectomy and partial resection of the jugular tubercle were performed, after which the foramen magnum was opened. Both cerebellar tonsils were lifted, and the caudal loops of the bilateral PICAs were isolated. Both vessels were temporarily clipped and anastomosed in a side-to-side fashion at the posterior medullary segment (PICA-PICA anastomosis) (Figure 1). The VA was subsequently occluded by clipping proximal and distal to the aneurysm. Finally, the PICA was occluded by clipping distal to the aneurysm with particular care to avoid the small vessels originating from the PICA.

RESULTS

Computed tomography (CT) performed on the first postoperative day revealed no new ischemic lesions in any cases. Postoperative cerebral angiography demonstrated patency of anastomosis and aneurysm regression in 5 cases. The remaining case (Case 2) developed recurrent hemorrhage from contralateral VA dissection on the second postop-

1 Clinical Summary

Case No.	Age (yrs)	Gender	H & K Grade	Time to Treatment	Postoperative Angiographic Findings	Complications	GOS	Follow-up Period
1	52	M	1	4 d	patent bypass, no aneurysm	none	GR	4 m
2	49	M	3	2 d	no patent bypass, no aneurysm, contralateral VA dissection	SAH, ruptured contralateral VA dissection	D	4 d
3	42	M	2	2 d	patent bypass, no aneurysm	Myopathy of bilateral quadriceps femoris muscles	MD	2 m
4	51	F	2	2 d	patent bypass, no aneurysm, growing contralateral VA dissection	none	GR	31 m
5	47	M	2	5 d	patent bypass, no aneurysm	none	GR	21 m
6	55	F	1a	28m	patent bypass, no aneurysm	none	GR	2 m

M = male, F = female, GOS = Glasgow Outcome Scale, An = aneurysm, H & K = Hunt & Kosnik, SAH = subarachnoid hemorrhage, d = days, m = months, GR = good recovery, MD = moderately disabled, D = dead, Cases 2 & 4 were previously reported by Otawara et al [16].

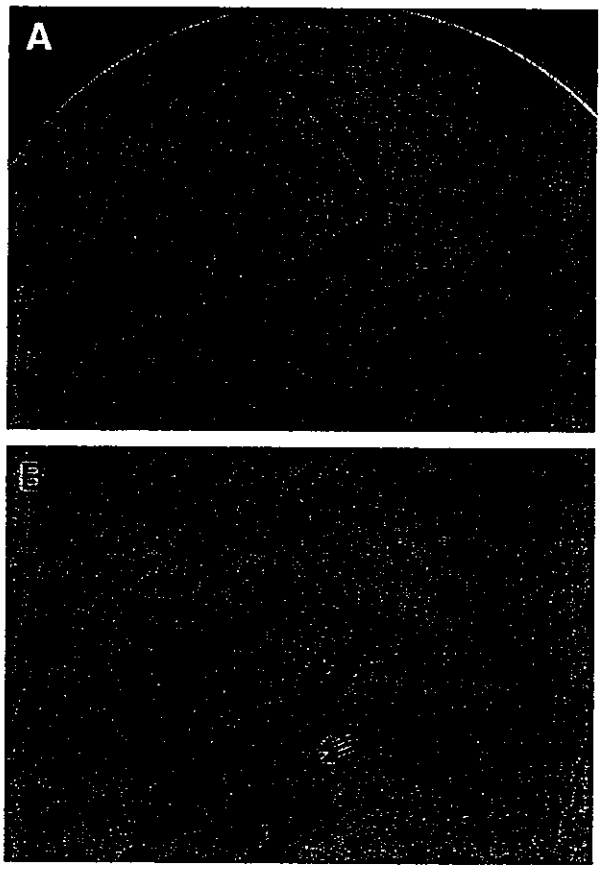
1 Intraoperative photograph showing a side-to-side anastomosis between the bilateral posterior inferior cerebellar arteries involving the caudal loop of those vessels (*arrows*) and cerebellum and medulla oblongata (*star*).

erative day and died on the fourth postoperative day [16]. Cerebral angiography performed immediately after the recurrent hemorrhage demonstrated occlusion of the contralateral VA because of arterial dissection. Therefore, the patency of the anastomosis could not be confirmed. All patients except Case 2 survived. However, one patient (Case 3) developed myopathy secondary to intraoperative compression by a fixed board and exhibited permanent lower extremity muscular weakness. No neurologic deficits were noted in the remaining four cases (Table 1).

Illustrative Case Report

CASE 6

A 55-year-old woman experienced sudden, severe headache. The patient was admitted to an outside institution and diagnosed with SAH. Cerebral angiography revealed a dissecting aneurysm of the left VA involving the origin of PICA. Intraoperative findings confirmed the presence of a dissecting aneurysm, and the left VA was surgically occluded by clipping proximal to the aneurysm. Follow-up cerebral angiography performed 25 months after the first operation demonstrated a remnant of the aneurysm. The patient was subsequently admitted to our institution. Right vertebral cerebral angiography revealed a fusiform aneurysm in the left VA (Figure 2A). A PICA-PICA anastomosis and left VA-PICA trapping were performed. Postoperatively, the patient developed transient paralysis of the left recurrent laryngeal and hypoglossal nerve. Cerebral angiography after the second operation showed a



2 Case 6. (A) Preoperative anteroposterior right VA angiogram demonstrating the left VA fusiform aneurysm in the distal portion of the origin of the posterior inferior cerebellar artery. (B) Postoperative anteroposterior right VA angiogram demonstrating a patent bypass (*arrows*) and regression of the aneurysm.

patent bypass and regression of the cerebral aneurysm (Figure 2B).

Discussion

Most groups have used the OA as a donor artery to revascularize the PICA [2,3,5,13,17,18,22]. However, dissection of the OA poses difficulties because the OA lies deep to the splenius capitis, longissmus capitis, suboccipital, and occipitalis muscles and is intimately attached to these structures by numerous vascular branches. Because the proximal OA is surrounded by a plexus formed by its companion veins, mobilization of the OA is difficult. In addition, water-tight dural closure is impossible.

Because of the depth and space constraints of the operative field, VA-PICA transposition [7] is a difficult and complicated procedure. The proximal segment of the PICA gives rise to several perforating vessels to the brainstem [15], further complicating PICA mobilization.

Other surgeons have described their experience with VA-STA/RA graft-PICA anastomosis [4,9,10]. The operative field is deep and narrow when the intradural VA is used as a donor, and water-tight dural closure is impossible if the extradural VA is used as a donor. Further, performing the anastomoses in two portions results in increased technical difficulty of the procedure.

The calibers of the posterior medullary segments of PICAs are relatively consistent. The proximity and parallel course of the bilateral caudal loops of the PICA greatly facilitate their mobilization and anastomosis to one another. The presence of one suture line and a short bypass segment are also desirable. However, areas perfused by the PICAs are theoretically placed at risk of ischemia during anastomosis, but this complication has not been observed [14,19].

Only 4 cases of PICA-PICA anastomosis have been reported [14,19]. Good clinical outcomes and anastomosis patency were seen in all of the previous cases. The present cases yielded similar results except for the presence of recurrent hemorrhage in one case and compression myopathy in another case.

CONCLUSION

PICA-PICA anastomosis is a useful procedure for the reconstruction of the PICA when parent vessel occlusion or trapping is necessary to exclude a VA aneurysm involving the origin of the PICA.

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COMMENTARY

Kakino et al describe the treatment of 6 patients who presented with subarachnoid hemorrhage from dissecting aneurysms that involved the vertebral artery and the posterior inferior cerebellar artery (PICA) with side-to-side PICA-PICA anastomosis and parent-vessel occlusion. We also use a side-to-side PICA-PICA anastomosis to treat aneurysms involving the PICA or vertebral artery or both [1]. As the authors mentioned, in situ bypasses have several advantages, including one suture line, a short bypass distance, and a close match in the caliber of the two anastomosed vessels. Although technically challenging, this technique can be an elegant solution for complex aneurysms.

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ELSEVIER

Aneurysm

ANXIETY BEFORE AND AFTER SURGICAL REPAIR IN PATIENTS WITH ASYMPTOMATIC UNRUPTURED INTRACRANIAL ANEURYSM

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Otawara Y, Ogasawara K, Kubo Y, Tomitsuka N, Watanabe M, Ogawa A, Suzuki M, Yamadate K. Anxiety before and after surgical repair in patients with asymptomatic unruptured intracranial aneurysm. Surg Neurol 2004;62:28–31.

BACKGROUND

Ruptured intracranial aneurysm is a serious condition with high mortality and morbidity. Patients notified of the presence of the unruptured intracranial aneurysm may become anxious because of the fear of rupture. We prospectively investigated the anxiety of patients with unruptured intracranial aneurysm before and after surgery.

METHODS

Thirty-seven patients with an asymptomatic unruptured intracranial aneurysm were enrolled, 13 men and 24 women aged 32 to 70 years (mean age, 57.2 years), who underwent surgical repair of the aneurysm. The anxiety of patients was assessed one month before and after surgery using the Japanese version of the State-Trait Anxiety Inventory.

RESULTS

The trait anxiety scores, which refer to stable personality factors reflecting the general level of fearfulness, did not change significantly after surgery. In contrast, the state anxiety scores, which refer to transient anxiety that varies according to the situation, decreased significantly after surgery ($p = 0.001$, paired t test). Only the preoperative high state anxiety scores among the multiple variables were associated with the significant decrease in state anxiety after surgery ($p = 0.0183$, logistic regression analysis).

CONCLUSIONS

The anxiety of patients with asymptomatic unruptured intracranial aneurysm significantly decreased after surgery. Anxiety of patients with asymptomatic unruptured intracranial aneurysm may deserve attention in deciding whether to treat the aneurysm.

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KEY WORDS

Anxiety, state-trait anxiety inventory, unruptured intracranial aneurysm.

Ruptured intracranial aneurysm is a serious condition with high mortality and morbidity, despite recent improvements in management. The mortality of ruptured intracranial aneurysm is 32 to 67%, with most patients dying of the initial bleeding or the immediate complications [3]. Approximately one-third of patients who survive the hemorrhage remain disabled, with loss of independence [3]. Therefore, treatment of intracranial aneurysms before rupture has attracted increasing interest.

Recently, a brain screening system called "Brain Check-up" has become widely used in Japan [7]. One of the purposes of this brain screening is to identify asymptomatic unruptured intracranial aneurysms (UIAs). Furthermore, new and improving neuro-imaging techniques including magnetic resonance angiography and computed tomography (CT) angiography can readily identify asymptomatic UIAs. On the other hand, from a patient's point of view, they might become anxious after the notification of the presence of UIAs because of fear for the rupture of their UIAs.

The present study prospectively evaluated the levels of anxiety before and after surgical repair of UIA.

METHODS

PATIENT POPULATION

This prospective study was based on a series of 75 consecutive patients who underwent surgical re-

pair of UIAs at the Department of Neurosurgery of the Iwate Medical University between January 1999 and February 2002. The inclusion criteria for this study were: UIA larger than 3 mm confirmed by CT angiography, magnetic resonance angiography, or digital subtraction angiography; complete surgical obliteration of the UIA; age no more than 70 years; and informed consent for this study. Exclusion criteria were: symptoms from compression by the UIA; previous premorbid psychiatric history; trapping or proximal occlusion of the UIA; incidentally found UIA with previous history of ruptured arteriovenous malformation, massive cerebral infarction, intracerebral hemorrhage, or aneurysmal subarachnoid hemorrhage (SAH); systemic diseases such as diabetes mellitus, renal failure, or heart disease; and multiple UIAs requiring multiple obliterations. Ethical approval was granted by the institution.

Preoperative vascular risk factors were as follows. Hypertension was defined as a diastolic blood pressure of more than 90 mm Hg, systolic blood pressure of more than 140 mm Hg, and/or the use of antihypertensive medication. Diabetes mellitus was defined as a fasting glucose level of more than 126 mg/dL and/or the use of antidiabetes medication. Hyperlipidemia was defined as a cholesterol level of more than 240 mg/dL and/or the use of cholesterol lowering medication.

Patients received an explanation of the risk of the UIAs as follows. The annual rupture rate of UIA is 2.3%, and the cumulative rupture rate is 20% at 10 years and 35% at 15 years after diagnosis, as found in a large series of patients [10]. Rupture of UIA has an overall mortality of 32 to 67% [3]. Approximately one-third of patients who survive the hemorrhage remain disabled, with loss of independence [3]. The surgical risk was explained to the patients based on the surgical mortality of 0% and surgical morbidity of 1.2% in our institution from January 1996 to December 1998.

ANXIETY TESTING

The anxiety of patients was assessed using the Japanese version of the State-Trait Anxiety Inventory (STAI), which was translated into Japanese from the original version of the STAI [9]. The reliability and validity of the scale are reported to be satisfactory [5]. The STAI is one of the methods for measuring the level of anxiety, and consists of 40 separate self-assessed items. The STAI has two parts: state anxiety (transient anxiety that varies according to the situation) and trait anxiety (stable personality factors reflecting the general level of fearfulness). High scores in the STAI imply high levels of anxiety. The STAI was performed one month before surgery, when patients were already notified of the presence, the natural history, the risk of rupture, and the surgical risks of the UIAs. The STAI was repeated 1 month after surgery.

DATA ANALYSIS

The relationship between pre- and postoperative STAI scores was assessed using the paired t test. If STAI scores changed significantly, multiple analyses using logistic regression analysis were performed to determine the effect of multiple variables (age, sex, hypertension, diabetes mellitus, hyperlipidemia, history of surgical operation, years of education, and preoperative trait and state anxiety) on the change in anxiety. Significant change in anxiety was defined as a difference in scores of 10 points or more in an individual patient before and after the surgery. P values less than 0.05 were regarded as significant.

RESULTS

Of the 75 surgically treated patients with UIAs in the examined period, 35 patients were excluded: 6 because of compression of cranial nerve or brain by the aneurysm, 20 because of incidentally found UIA with ruptured arteriovenous malformation, massive cerebral infarction, intracerebral hemorrhage, and aneurysmal SAH, and 9 with multiple UIAs. Three patients refused to participate in this study. Thus, 37 patients were enrolled for this study, 13 men and 24 women aged from 32 to 70 years (mean 57.2 years).

Hypertension, diabetes mellitus, hyperlipidemia, and history of operation were present in 21, 5, 7, and 24 patients, respectively. The participants had a mean education period of 11.4 years. The UIA was located on the internal carotid artery in 11 patients, the middle cerebral artery in 16 patients, the anterior cerebral artery in 8 patients, and the vertebrobasilar artery in 2 patients. No operative complications were observed, and all patients returned to their previous lives' activities.

The state anxiety scores significantly decreased ($p = 0.001$) after surgery, whereas the trait anxiety scores did not change (Table 1). The state anxiety scores postoperatively decreased by 10 points or more in 21 of 37 patients, and changed less than 10 points in the remaining 16 patients. No patient exhibited a postoperative increase of 10 points or more in the state anxiety scores. Only the preoperative high state anxiety scores among the multiple variables were associated with the significant de-

1 State and Trait Anxiety Inventory Scores

	BEFORE SURGERY	AFTER SURGERY	*P* VALUE
State anxiety	48.3 ± 10.3	41.5 ± 9.9	0.001
Trait anxiety	43.6 ± 11.4	42.1 ± 9.4	NS

Values are mean ± standard deviation. NS: not significant

crease ($p = 0.0183$) in state anxiety after surgery in logistic regression analysis (Table 2).

DISCUSSION

Our results indicate that the anxiety of patients with UIA significantly decreased after surgery. High preoperative state anxiety scores were the greatest factor in the decreased state anxiety after surgery.

STAI is a popular instrument for measuring anxiety. It has been used previously in many researches on emotional reactions to surgery [6]. It is written at a sixth grade reading level and can be completed in approximately 10 minutes. This questionnaire consists of 40-items self-report rating scale and has 2 parts: the State Scale and the Trait Scale. The State Anxiety Scale assesses feelings of apprehension, tension, nervousness, and worry in terms of how respondents feel "right now." For the 20 questions on this scale, possible responses are: "not at all," "somewhat," "moderately so," and "very much so." The Trait Anxiety Scale reflects how people "feel generally," all the time. It includes statements such as "I am a steady person" or "I am nervous." Possible answers for these 20 items are: "almost never," "sometimes," "often," and "almost always."

State anxiety before surgery might derive from fear of rupture of the UIA and the possible surgical complications. After surgery, the patients were informed of the obliteration of the UIA and the absence of surgical complications. Such information is likely to decrease state anxiety after surgery. It is supported by the logistic regression analysis that only preoperative state anxiety affected the significant decrease in the score of state anxiety. In contrast to the significant decline in state anxiety scores after surgery , trait anxiety scores did not change. These results are consistent with previous findings that trait anxiety did not change in response to situational stress and is not affected by surgery [8].

The international study of UIAs (ISUIA), by far the largest study of its type to date, recently reported a considerably lower rupture rate of UIAs and higher rate of surgical complications than those in previous studies [4]. However, the information given to the patients in our study was not based on the ISUIA report, because it included a selection bias of the patients that lead to low rate of rupture of UIA and high rate of surgical complication [1]. Instead, patients enrolled in our study were informed of an annual rupture rate of 2.3%, which was based on another report, [10] and a surgical morbidity of 1.2%, which was based on the surgical results at our institution. It might be the limitation of this study that the information of the annual rupture rate of 2.3% may have caused a higher level of anxiety, compared to the rate of the ISUIA report.

There are other limitations of this study. First, the preoperative anxiety was evaluated after the notification of the presence, the natural history, the risk of rupture, and the surgical risks of the UIAs, which may affect the preoperative anxiety. Secondly, we cannot distinguish the fear of rupture of the UIA and the fear for possible surgical complications as the contribution to the preoperative high level of state anxiety. Further examination is required for the evaluation of the anxiety before and after the notification of that information to patients.

2 Logistic Regression Analysis of Decreases in State Anxiety

VARIABLES	DECREASE IN STATE ANXIETY		*P* VALUE
	YES (N = 21)	NO (N = 16)	
Age (yr)	57.7 ± 8.8	56.8 ± 9.7	NS
Male	6	7	NS
Hypertension	9	12	NS
Diabetes mellitus	1	4	NS
Hyperlipidemia	5	2	NS
History of operation	11	13	NS
Education year (yr)	11.2 ± 2.9	11.6 ± 2.6	NS
Preoperative trait anxiety	43.2 ± 11.4	44.6 ± 12.7	NS
Preoperative state anxiety	53.5 ± 8.2	46.2 ± 10.8	0.0183

Values are mean ± standard deviation. NS: not significant

The optimal management of patients with UIAs remains controversial. The natural history of UIAs and treatment outcomes are influenced by patient factors, such as previous aneurysmal SAH, age, and coexisting medical conditions; aneurysm characteristics, such as size, location, and morphology; and factors in management, such as the experience of the surgical team and the treating hospital [2]. We believe that the anxiety of patients with UIA also deserves attention in deciding whether to treat a UIA.

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眼で見る 神経内科

限局性に硬膜が造影された特発性低髄液圧症候群*

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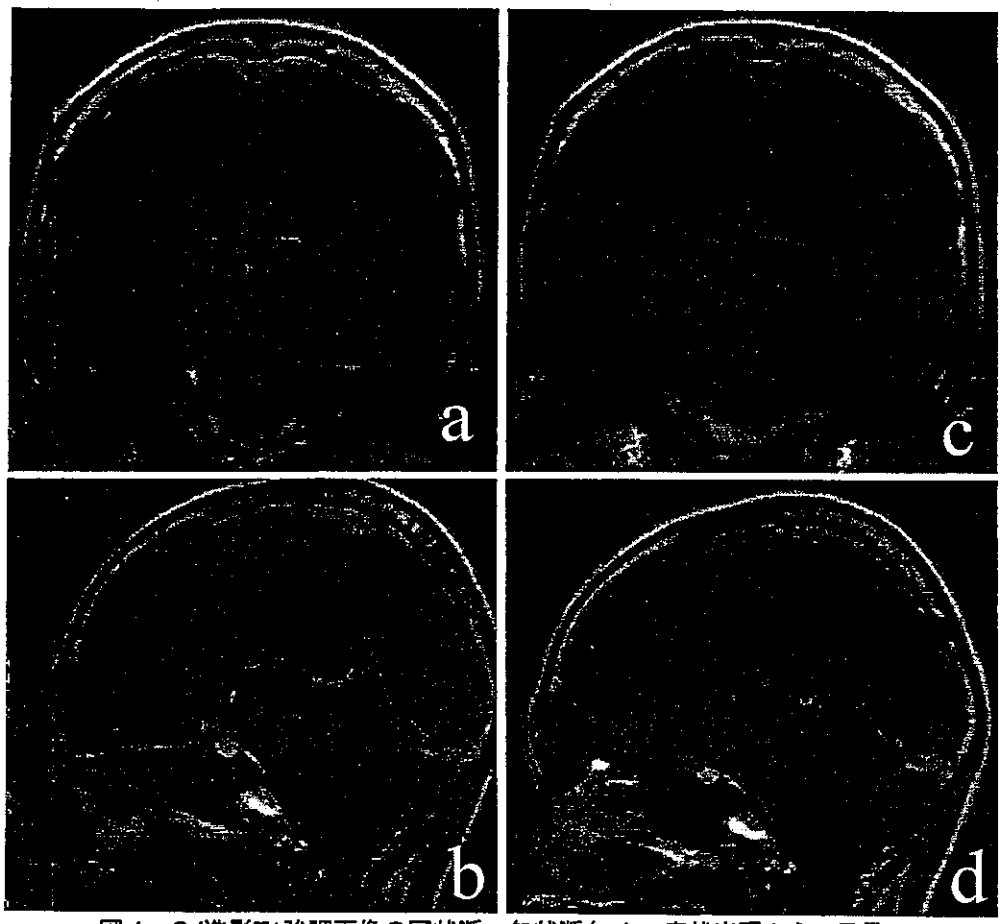

図1 Gd造影T1強調画像の冠状断，矢状断(a, b：症状出現から7日目，c, d：症状出現から13日目)

低髄液圧症候群は起立性頭痛を生じ，硬膜損傷の既往のない自然発症例に対してspontaneous intracranial hypotension(SIH)という名称が用いられている[1]．SIHの診断基準は，①髄液圧が低く60mmH$_2$O以下，②硬膜穿刺の既往がない，③髄液は正常であることが多いが，赤血球が混じ

* MRI findings of spontaneous intracranial hypotension.(Accepted April 6, 2004).

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たり，蛋白上昇，リンパ球増多，キサントクロミーがみられたりすることがある，④硬膜下水腫がみられることがある，⑤症状は通常2週間から数ヵ月以内に自然寛解すること，などがあげられている[1]．

症例は17歳，男性である．起立性頭痛が出現し，5日目に近医を受診し髄液検査を施行され，髄膜炎は否定された(髄液圧は不明)．その後も症状は改善せず，当院紹介となった．項部硬直を含め神経学的異常所見は認めなかった．低髄液圧症候群が疑われたが症状増悪の可能性を考え髄液検査は行わなかった．症状出現から7日目に造影MRIを行ったところ頭頂部の硬膜に造影効果を認めた(図 1-a, b)．症状が持続するため入院の上，安静，補液を行った．徐々に起立性頭痛は改善した．症状出現から13日目には症状は消失しており，造影MRIを再検したところ造影効果は消失していた(図 1-c, d)．本性例の原因として硬膜損傷の既往がないことから特発性としたが，髄液漏出の可能性も否定できない．

造影MRIではガドリニウムにより硬膜が瀰漫性に造影される特徴所見が多数報告されている．硬膜内膜ではtight junctionが欠如し血液脳関門が存在しないため，拡張した微小血管あるいは間質にガドリニウムが貯留し造影される[2]．また，髄液内圧低下を改善させようとして髄膜内血管の代償性拡張が起こり拡張した血管が強く造影される[3]．血管造影で静脈の拡張を認めた症例の報告もある[4]．本症例は，頭頂部に限局した造影効果を認め，速やかに改善した．このことからやはり硬膜の炎症性変化ではなく血管拡張により造影されていたことが考えられる．SIHは一般に瀰漫性に硬膜の造影効果を認めることが多いが，本症例では限局性であったことが特徴であり，診断には水平断だけでなく，冠状断，矢状断を含めた撮影が必要である．

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<Abstract>

MRI findings of spontaneous intracranial hypotension.

by

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We here report a 17-year-old man with orthostatic headache. Dura matter on parietal lobes was locally enhanced on coronal and sagittal Gd-enhanced T1-weighted MRI. He was improved with infusion and rest. Diagnosis of spontaneous intracranial hypotension needs not only axial but also coronal and sagittal Gd-enhanced T1-weighted MRI.

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症例報告

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大腸癌を伴う慢性肥厚性硬膜炎を呈した血液透析患者の1例

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key words:眼筋麻痺,眼瞼下垂,多発脳神経麻痺,大腸癌,慢性肥厚性硬膜炎

〈要旨〉

症例は70歳男性.1999年より透析療法を導入(原疾患不明)された.2001年1月より頭痛が出現し,4月上旬より複視,視力低下,両側眼瞼下垂が加わったため当院に転院した.入院時,視力は光覚弁で,視神経萎縮,両側眼瞼下垂を認めた.眼球は正中に固定し,対光反射は消失しており,II・III・IV・VIの多発脳神経麻痺を認めた.頭部MRIでガドリニウム造影にて両側側頭葉,小脳テント,頭蓋底の硬膜の肥厚を認め,肥厚性硬膜炎と診断した.視力低下が急速に進行し光覚弁の状態となったため,メチルプレドニゾロン1,000 mgによるパルス療法を施行した.その後,大腸内視鏡を施行しBorrmann 2型の大腸癌を認めた.大腸癌は転移を認めず手術適応と判断し,Hartmann手術を施行した.術後に,視力は光覚弁から手動弁まで改善し,左眼の外転運動が可能となった.本例の特徴は大腸癌を伴い,手術後に臨床症状の改善を認めたことである.悪性腫瘍が肥厚性硬膜炎の原因と考えられ,さらに透析患者に合併した症例はまれであり貴重な症例と考え報告した.

A case of hypertrophic pachymeningitis concurrent with colorectal cancer in a patient on hemodialysis

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A 70-year-old patient was referred to our hospital for evaluation of ocular disorders. The patient has been on hemodialysis since 1999, but the underlying renal disease causing chronic renal failure remains unknown. He developed a headache in January 2001, followed by diplopia, reduced visual acuity and bilateral ptosis of the eyelid from April 2001. He was then referred to us for evaluation. The patient was admitted immediately. Examinations at admission showed absence of light sensation, atrophy of the optic nerve, and bilateral ptosis of the eyelids. The eyeballs were fixed at the center and there was no reaction to light. Multiple cranial nerve palsies involving the 2nd, 3rd, 4th, and 6th nerves were diagnosed. Cranial MRI with Gd contrast imaging demonstrated hypertrophy of the dura mater in bilateral temporal lobes, the cerebellar tent, and skull base. We diagnosed his condition as hypertrophic pachymeningitis. The symptoms progressed rapidly until blindness developed. Pulse therapy with methylprednisolone 1,000 mg was conducted. Subsequently, colorectal endoscopy demonstrated the presence of colorectal carcinoma of Borrmann type 2. Since there was no metastasis of colorectal cancer detected, surgery was considered to be indicated and Haltmann procedure was performed. Postoperatively, visual acuity was improved from light perception to hand motion, and slight abduction became possible in the left eye. In this patient with hypertrophic pachymeningitis concurrent with colorectal carcinoma, the majority of the physical findings described above were resolved or mitigated by surgical removal of the cancer. The malignant tumor was considered to have been the cause of hypertrophic pachymeningitis. Since the occurrence of these concurrent conditions in a patient on hemodialysis is extremely rare, we documented this case.

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緒　言

肥厚性硬膜炎は，脳硬膜の慢性炎症を伴う肥厚性変化により頭痛，多発脳神経麻痺，けいれん発作，運動失調などさまざまな症状を呈する疾患である．近年，画像検査の進歩により診断される確率が高くなっている．本症は，病因として感染症，膠原病，血管炎，外傷，薬剤性，悪性腫瘍などの基礎疾患が報告されているが，原因不明のものも多く，特発性として報告されている．今回われわれは，視力障害，両側眼瞼下垂，両側外眼筋麻痺など多発脳神経麻痺，頭痛で発症し，大腸癌に伴う肥厚性硬膜炎と考え，大腸癌摘出術を施行し，その後臨床症状が改善した維持血液透析患者の症例を経験したので報告する．

I．症　例

患者：70歳，男性．

主訴：視力低下，眼瞼下垂，複視．

現病歴：1999年11月24日，全身浮腫，尿毒症症状が出現し原疾患不明の末期腎不全に陥り，透析療法を導入，開始された．2000年7月より無症状であったがCRPが7～8 mg/dLと持続的に陽性となった．2001年1月頃より頭痛が出現し，4月上旬より複視を訴え，眼瞼下垂が出現した．眼症状はさらに進行し，同月下旬より視力が低下した．5月上旬には，両側眼瞼下垂および眼球運動障害が著明になった．眼球は正中に固定し，視力は光覚弁に低下したため，5月10日当院に転院となった．

既往歴：2000年1月帯状疱疹．

家族歴：特記すべきことなし．

現症：身長168 cm，体重59 kg，体温36度，血圧200/80 mmHg，90/分，神経学的所見：意識は清明，脳神経系では視力は光覚弁であり眼底検査にて視神経萎縮が確認された．両側眼瞼下垂のためほぼ閉眼状態となり，眼球は正中固定し，対光反射は消失しており，II・III・IV・VIの多発脳神経麻痺を認めた．その他の脳神経系には明らかな異常所見はみられなかった．四肢には筋力低下，筋萎縮，感覚障害は認めなかった．協調運動は正常であり，歩行も可能であった．腱反射に異常なく，髄膜刺激症状も認めなかった．

検査所見：CRP 14.6 mg/dL，WBC 11,700/mm³，血沈84 mm/hrと炎症反応の上昇を認めた．血清梅毒反応陰性，ACE，リゾチームは正常範囲であった．免疫グロブリン，各種自己抗体，血清補体価に異常なく，p-ANCA，c-ANCAは陰性であった．甲状腺ホルモン値も正常で，HbA1c 4.7と正常範囲内であった．腫瘍マーカーはCA19-9 375 U/mLと上昇していた．

髄液所見：初圧140 mmHg，細胞数1 mm³（リンパ球），蛋白38 mg/dL，糖67 mg/dL（血糖92 mg/dL），Cl 129 mEq/Lと異常なく，細菌・真菌・結核菌培養は陰性であった．髄液細胞診はclass Iで異常細胞は検出されなかった．

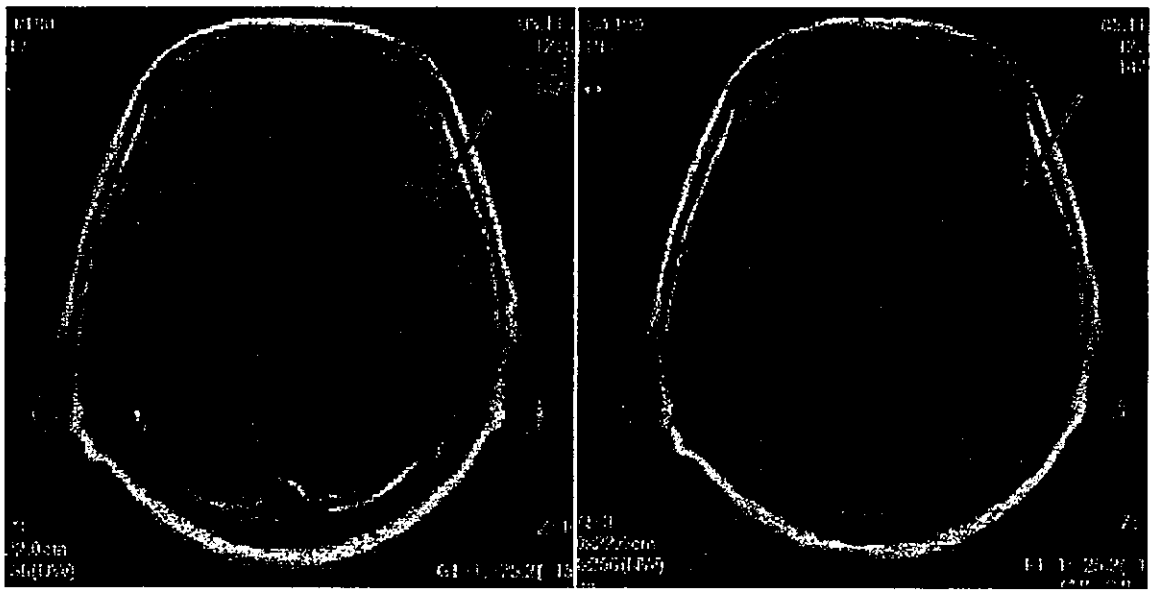
頭部MRI（図1）：ガドリニウム造影にて両側側頭葉，小脳テント，頭蓋底の硬膜の造影を認め，同部位の硬膜の肥厚を認めた．

臨床経過（図2）：頭部MRIにて硬膜の肥厚像を呈し，ガドリニウムにて硬膜の造影を認めたため肥厚性硬膜炎と考え，それに伴う多発脳神経麻痺と診断した．急速に視力が低下し光覚弁の状態となったため，諸検査では原因を明らかにしえなかったが，症状の進行あり，治療を優先しメチルプレドニゾロン1,000 mgによるパルス療法を施行した．治療ののち，軽度眼瞼下垂の改善を認め，開眼可能となった．その後，下血が出現し，血便が持続したため大腸内視鏡を施行したところ，直腸にBorrmann II型の大腸癌の存在が確認された．直腸の大腸癌部位より出血が持続し貧血が進行し，さらに播種性血管内凝固症候群が合併した．血小板，濃厚赤血球の輸血を行い，メシル酸ナファモスタットを投与し保存的加療を行った．大腸癌は画像所見にて転移を認めず手術適応と判断し，全身状態が安定した段階で，6月29日大腸癌摘出術としてHartmann手術を施行した．術後，眼瞼下垂が改善し，視力は光覚弁から手動弁まで改善した．さらに，左眼の外転運動が可能となった．術後のためステロイドの追加投与は行わなかった．

II．考　察

肥厚性硬膜炎は何らかの原因により脳硬膜の炎症と線維性の肥厚を生じ，硬膜の著明な肥厚を特徴とする疾患である．主に，頭蓋底部，小脳テント，穹隆部が好発部位である．症状として慢性頭痛，多発脳神経麻痺，運動失調，けいれんなどを認め，眼窩上の硬膜肥厚では視神経障害が生じやすい[1]．これらの症状は硬膜の肥厚により神経が直接圧迫されて生じるものと，血管の圧迫により生じる二次的なものとに分けられる．

本例の症状は，頭痛と多発脳神経麻痺として両側II，III，IV，VIの完全麻痺を認めた．頭部MRIにて頭蓋底の硬膜の肥厚を認め，慢性肥厚性硬膜炎と考えられた．



T1強調画像　Gd造影　　T1強調画像

図1　頭部MRI画像．両側側頭葉，小脳テント，頭蓋底の硬膜の肥厚を認め，同部分は，ガドリニウムで造影を認める．

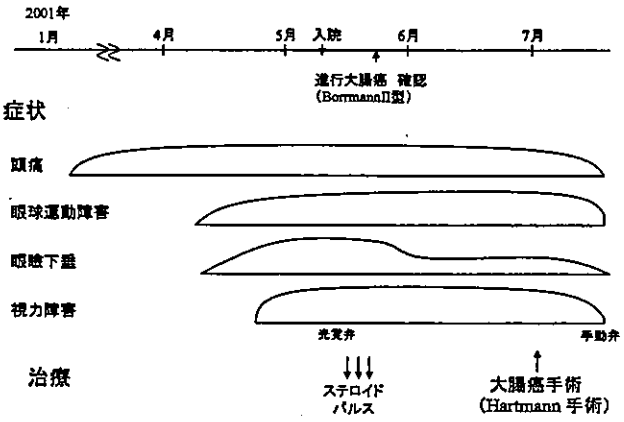


図2　臨床経過

本例の特徴は大腸癌を伴っており，大腸癌の手術ののち，臨床症状の改善を認めたことである．このことから大腸癌が肥厚性髄膜炎の原因に関連していることが示唆された．肥厚性硬膜炎の原因としては細菌，梅毒，結核，真菌，サルコイドーシス，Wegener肉芽腫症，慢性関節リウマチ，全身性エリテマトーデス，混合性結合組織病，神経ベーチェット，血管炎症候群，悪性リンパ腫，髄膜腫，外傷，薬剤性などが報告されているが原因不明であるものも少なくない[2]．また，近年，p-ANCA陽性の肥厚性硬膜炎が報告されてきており[3]，抗核抗体陽性，リウマチ反応などの自己抗体が陽性であることから，本症の発症に自己免疫が関連している可能性が推察されている[3]．本例においては各種培養，自己免疫抗体，p-ANCA，ACE，リゾチームなどを測定したが異常所見は認められなかった．詳細なメカニズムは明確にされていないが，何らかの炎症が惹起されたあと，硬膜に対する自己免疫機序が働き硬膜の持続的な慢性炎症をきたしている可能性が示唆されている．本例でも同様の機序にて，大腸癌に伴う何らかの自己免疫因子を介し炎症を引き起こしている可能性があると推測される．

悪性腫瘍が肥厚性硬膜炎の原因と考えられた症例はごく少数報告されている．Paakkoら[4]はGd-DTPAにて硬膜の造影を認めた悪性腫瘍を有する14例について検討している．悪性腫瘍は前立腺，リンパ腫，乳癌，卵巣癌で，このうち，髄液細胞診で悪性細胞を認めたものは3例，頭蓋骨転移または骨シンチで異常陰影を5例に認めた．髄液所見は軽度の蛋白上昇や細胞数増加や糖の低下を認めた例もあるが非特異的で，6例では異常を認めなかったとしている．Riverら[5]は，MRIで硬膜の肥厚を20例に認め，13例に大腸癌，前立腺癌，乳癌などの悪性腫瘍を認めたと報告している．これらでは，高率に頭蓋骨転移を認めており，悪性腫瘍の転移，直接浸潤による硬膜肥厚と考えられた．硬膜生検をされた例では，肥厚した硬膜にリンパ球，形質細胞，線維芽細胞などの炎症細胞に加えて類上皮細胞，多核巨細胞，好中球やリンパ濾胞なども認められているが，非特異的な所見であるとされる．いずれにしても，硬膜肥厚がおこりうる詳細なメカニズムに関しては明らかにされていない．本例では，髄液は正常で細胞診でも異型細胞は認めず，MRI所見などからも悪性腫瘍の硬膜への直接浸潤の可能性は低いと思われたが，硬膜生検は実現できなかったため詳細は不明と

言わざるをえない．

治療は，一般的には結核や真菌症，副鼻腔炎，中耳炎などの感染症が明らかである場合，感染症の治療が優先される．特発性の場合，副腎皮質ステロイドが最も多く使用されている．また基礎疾患に膠原病，肉芽腫性疾患，血管炎症候群，自己抗体陽性，p-ANCA 陽性などの場合もステロイド治療が優先される．ステロイド剤に反応が乏しい例や使用できない場合はアザチオプリンやシクロホスファマイドなどの免疫抑制剤が考慮されている．本例は悪性腫瘍の関与はあったもののステロイドのパルス療法を施行し軽度改善がみられた．このことからも，何らかの免疫学的機序が関与していた可能性が示唆される．さらに手術にて腫瘍摘出後に症状の改善を認めたことより，悪性腫瘍の存在が症状を惹起していた可能性が考えられる．

本例は血液透析（HD）施行中であるが，過去に HD 施行中に慢性肥厚性硬膜炎と診断された症例は 2 例報告されている[6,7]．Feringa ら[6]は HD 中の患者が，視力障害をきたし失明に至った肥厚性硬膜炎の一例を報告している．原因として感染症，膠原病など検索されたが有意所見は得られず，脳出血により死亡し，剖検にて厚く肥厚した硬膜を認めた．病理学的にはリンパ球を含んだ慢性の炎症細胞の肥厚硬膜部位への浸潤像のみで非特異的な所見であった．また，田島ら[7]も HD 中の 66 歳女性に発症した肥厚性硬膜炎の一例を報告しているが，この症例は p-ANCA 陽性であった．ステロイド剤によって p-ANCA が低下したことより，発症には p-ANCA を含めた免疫学的機序が関与していると考察している．HD と慢性肥厚性硬膜炎との関連性については不明であり，偶発的な合併であるのか，HD 例には何らかの免疫的機序により罹患しやすいのかは，今後の症例の蓄積が望まれる．

本症例では，その後透析方法の変更も行わず，投与薬の変更もなく症状の改善が持続した．大腸癌切除，ステロイド剤の投与は症状改善に寄与した可能性が高いと考えられた．

慢性肥厚性硬膜炎は多彩な原因により発症することが知られているが，原因不明のものも多く，病因の一つとして悪性腫瘍も関与しうることを考慮する必要があると考えられる．慢性的な頭痛を伴い軽度炎症反応陽性例などには，このような病態の可能性も考慮し頭部 MRI 特に造影 MRI が有用であると考えられた．

結　語

視力障害，両側眼瞼下垂，外眼筋麻痺などの多発脳神経麻痺で発症した，慢性肥厚性硬膜炎を呈した維持血液透析患者の一例を経験した．大腸癌を合併していたため大腸癌摘出術を施行し，術後に，視力は光覚弁から手動弁まで改善し，左眼の外転運動が可能となり臨床症状の改善を認めた．このことから，悪性腫瘍に伴う何らかの因子により，自己免疫機序が作用し硬膜の肥厚をきたした可能性が示唆された．悪性腫瘍が肥厚性硬膜炎の原因と考えられ，さらに透析患者に合併した症例はまれであり貴重な症例と考え報告した．

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Association of the insertion/deletion polymorphism of the angiotensin I-converting enzyme gene in patients of migraine with aura

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Abstract

Recently, several angiotensin I-converting enzyme (ACE) inhibitors and an angiotensin II receptor blocker were demonstrated to have a clinically important prophylactic effect in migraine. ACE is one of the key enzymes in the rennin–angiotensin–aldosterone system, which modulates vascular tension and blood pressure. In humans, serum ACE levels are strongly genetically determined. Individuals who were homozygous for the deletion (D) allele showed increased ACE activity levels. To investigate the role of ACE polymorphism in headache, we analyzed the ACE insertion (I)/deletion (D) genotypes of 54 patients suffering from migraine with aura (MwA), 122 from migraine without aura, 78 from tension-type headache (TH), and 248 non-headache healthy controls. The ACE D allele were significantly more frequent in the MwA than controls ($p < 0.01$). The incidence of the D/D genotype in MwA (25.9%) was significantly higher than that in controls (12.5%; $p < 0.01$; odds ratio = 5.26, 95% confidence interval: 1.69–16.34, adjusted for age and gender). No differences in the remaining groups were found. Our results support the conclusion that the D allele and the D/D genotype in the ACE gene is a genetic risk factor for Japanese MwA. There seems to be a possible relationship between ACE activity and the pathogenesis of migraine.

Keywords: Angiotensin-converting enzyme (ACE); Substance P; Migraine; Headache; Polymorphism; Association

The pathophysiology of migraine is not yet fully understood but may involve painful vasodilatation of cerebral blood vessels and/or the release of vasoactive neurotransmitters from the perivascular axons in the dura mater after activation of the trigeminovascular system [7]. Moskowitz [7] proposed the "trigemino-vascular theory" of migraine headache, which claims that neurogenic inflammations of meningeal blood vessels are evoked by excitation of trigeminovascular fibers. Angiotensin I-converting enzyme (ACE) is one of the key enzymes in the rennin–angiotensin–aldosterone system, which modulates vascular tension and blood pressure. In humans, serum ACE levels are strongly genetically determined [3]. It has been reported that insertion (I)/deletion (D) polymorphism in the ACE gene was related to serum ACE levels. ACE levels in the subjects of D/D genotype may be higher than I/I genotype and ACE in the subjects of I/D genotype may be intermediate levels [11,18]. ACE D/D genotype has been frequently, though controversially, linked to cerebrovascular disorders [6,15]. Migraine is in part associated with cerebral circulation. In this present study we have investigated the possible contribution of this polymorphism in Japanese patients with migraine and tension-type headache (TH).

This study consisted of 54 patients suffering from migraine with aura (MwA), 122 from migraine without aura (MoA), and 78 from chronic TH (Table 1). The diagnosis of headache was made following the International Headache Society (IHS) criteria [5]. Two hundred forty-eight normal

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Table 1
Profile of subjects

	Cases	Males/females	Average age years ± S.D.
Controls	248	76/172	67.3 ± 11.7
MwA	54	17/37	33.1 ± 10.3
MoA	122	19/103	35.9 ± 13.4
TH	78	19/59	48.8 ± 18.0

healthy volunteers composed the control group. Control subjects have not suffered from migraine or tension-type headache in one's life. All the subjects were Japanese and gave their informed consent to the study.

A polymerase chain reaction (PCR) was performed on the genomic DNA samples with a GeneAmp PCR kit (Perkin-Elmer/Cetus) and primers as previously reported [12]. The PCR product is a 190-bp fragment in the absence of the insertion (D allele) and a 490-bp fragment in the presence of the insertion (I allele). In order to prevent from mistyping of the I/D genotype as D/D, we performed additional PCR using an insertion-specific primer pair with 5% dimethyl sulfoxide (DMSO) and confirmed ACE genotypes as previously reported [8]. The PCR fragments were electrophoresed in 2% agarose gels and stained with ethidium bromide. The differences in the frequency of ACE alleles and genotypes between groups were evaluated by the gene-counting method and comparison of groups by the χ^2 test. The level of significance was set at $p < 0.05$. The odds ratios associated with each genotype of ACE and their 95% confidence intervals were determined by using unconditional logistic regression. Statistical analyses were performed using SPSS version 11.0 for Windows (SPSS Inc., Chicago, IL, USA).

ACE I/D allele and genotype frequencies are given in Tables 2 and 3. The distribution of ACE genotypes in patients and controls did not deviate significantly from Hardy–Weinberg equibrium. The ACE D allele was significantly more frequent in the MwA than controls. We detected that the incidence of the D/D homozygous genotype in MwA was significantly higher than that in controls. No differences in the remaining groups were found.

Recently, migraine has been shown to have a partly genetic basis. Point mutations in the voltage-dependent P/Q-type Ca^{2+} channel alpha 1A subunit (CACNA1A) gene have been identified in familial hemiplegic migraine (FHM1), which is linked to chromosome 19p13 [9]. Another form of familial hemiplegic migraine (FHM2) is caused by mutation in the gene encoding the alpha-2 subunit of the sodium/potassium pump (ATP1A2), which is linked to chromosome 1q23 [4]. These specific migraines are rare forms and are caused by mutations in single genes. On the other hand, it is unlikely that "normal" migraine is caused by a single gene abnormality. Rather, it is probably caused by multifactorial genetic factors and environmental factors including foods and their life-style. Although non-genetic factors play a role in migraine, family and twin studies demonstrated that migraine, especially MwA, had a strong genetic component [13].

Table 2
The allele frequency of the ACE I/D polymorphism for headache sufferers

	Allele frequency		OR	95%CI	p value
	D	I			
Controls	176(35)	320(65)			
MwA	54(50)	54(50)	1.82	1.20–2.76	<0.01
MoA	98(40)	146(60)	1.22	0.89–1.67	0.22
TH	65(42)	91(58)	1.30	0.90–1.88	0.16

Figures in parentheses indicate percentages. D: deletion allele; I: insertion allele; OR: odds ratio; CI: confidence interval.

There was a report of the positive association with the D/D genotype and MoA in white subjects who were born in Sicily [10], but there was no data and comments with MwA. They also demonstrated a strong association between plasma ACE activity and the ACE I/D polymorphism [10]. Our data suggest that the D allele and the D/D genotype in the ACE gene is a genetic risk factor for Japanese MwA, but not for MoA. We have no data to clarify of this point, but several authors pointed out a significant ethnic differences in the frequency of the I/D polymorphism as well as the associated ACE activity. This is the first report that demonstrates a clear association of a common ACE mutation with Japanese migraineur.

ACE is also able to inactivate bradykinin and substance P, a potent vasodilatator [16,17]. Substance P is suggested one of the neurotransmitters in the "trigemino-vascular theory". Few studies have investigated the relationship between the ACE genotype and substance P. Arinami et al. [1] reported higher substance P levels in brain contents with the D/D genotype of ACE gene, and this is the opposite tendency, might be expected. The exact mechanism of the relationship between substance P and ACE genotype is still unknown. The alternation of ACE activity due to the I/D polymorphism would result in changed levels of the neurotransmitters and vulnerability to cranial vascular activity. These states appear to be analogous to those found during migraine headache or aura.

In addition, several ACE inhibitors and an angiotensin II receptor blocker were demonstrated to have a clinically important prophylactic effect in migraine. First, Bender [2] reported to have successfully treated with an ACE inhibitor for prophylaxis of migraine in a small group. Then, one of the ACE inhibitor, lisinopril, was demonstrated to have a clinically important prophylactic effect in migraine with a randomized, placebo controlled, crossover study [14]. Moreover, the angiotensin II receptor blocker, candesartan, also provided effective migraine prophylaxis with a randomized controlled trial [19]. These trials suggested that the rennin–angiotensin–aldosterone system must be concerned at least in part with the pathogenesis of migraine.

We conclude that the D allele and the D/D genotype of ACE gene are a genetic risk factor for MwA. In this study, ACE circulating levels in controls and headache subjects have not examined. Since our data was only designed to estimate the frequency of ACE genotype, we have no definite information on the etiology of difference between MwA and MoA. There seems to be a possible relationship between ACE activity and the pathogenesis of migraine, according to our results.

Table 3
The ACE I/D genotype and odds ratios for headache sufferers

	Genotype	n	Not adjusted			Adjusted for age and gender		
			OR	95%CI	p trend	OR	95%CI	p trend
Controls	I/I	103(42)						
	I/D	114(46)						
	D/D	31(12)						
MwA	I/I	14(26)	1			1		
	I/D	26(48)	1.68	0.83–3.39	0.15	1.62	0.66–3.97	0.29
	D/D	14(26)	3.32	1.43–7.72	<0.01	5.26	1.69–16.34	<0.01
MoA	I/I	43(35)	1			1		
	I/D	60(49)	1.26	0.79–2.02	0.34	1.11	0.56–2.20	0.77
	D/D	19(16)	1.47	0.75–2.88	0.26	1.96	0.76–5.06	0.16
TH	I/I	26(33)	1			1		
	I/D	39(50)	1.36	0.77–2.38	0.29	1.03	0.55–1.93	0.92
	D/D	13(17)	1.66	0.76–3.61	0.20	1.67	0.70–3.98	0.25

Figures in parentheses indicate percentages. D: deletion allele; I: insertion allele; OR: odds ratio; CI: confidence interval.

Further studies with larger samples must be undertaken concerning the relationship between the ACE and headache.

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