表3 一次性頭痛プラス二次性頭痛と診断する要件

1．原因疾患と頭痛とが時期的に一致していること
2．一次性頭痛の頭痛の著しい悪化のあること
3．原因疾患が一次性頭痛を悪化させたという確実な証拠のあること
4．原因疾患軽快後にその頭痛の改善または消失があること

混乱が生ずる．そこで一次性頭痛，二次性頭痛の名称を採用することにした．episodic は「反復発作性」から「反復性」に，「前兆を伴う片頭痛」，「前兆を伴なわない片頭痛」は「前兆のある片頭痛」や「前兆のない片頭痛」と簡素化した表現を採用した．

新国際頭痛分類（ICHD-Ⅱ）の注意点

これまで流布している「混合型頭痛」（多くは片頭痛プラス緊張型頭痛）の頭痛病名は採用されていない．頭痛のタイプは別々に診断しコード化されるべきである．例えば重症の慢性頭痛患者は，1．1「前兆のない片頭痛」，2．2「頻発反復性緊張型頭痛」，8．2「薬物乱用頭痛」の三つの診断がつくこともある．その際には重要な順に記載する．患者がある時期に一つの診断を受け，その後に他の頭痛診断を受けることもある．一次性頭痛プラス二次性頭痛のこともありうる．その要件は表3に示す．二つ以上の頭痛タイプが存在するときには，頭痛日記の記録が勧められる．頭痛日記は診断と治療の向上に役立つ．

これまで臨床的に頻用されてきた慢性連日性頭痛（CDH）は新分類でも採用されていない．発作頻度の極めて高い片頭痛は1．5．1「慢性片頭痛」か8．2「薬物乱用頭痛（MOH）」プラス「片頭痛」のいずれかである．もし鎮痛薬やトリプタンなどの薬剤乱用がある場合には，初診時には ① 片頭痛，② 慢性片頭痛の疑い，③ 薬剤乱用性片頭痛疑いの三つの診断がつけられる．その後2ヵ月間薬剤を中止しても，なおかつ片頭痛が慢性的に起る場合に，1．5．1「慢性片頭痛」と診断される．慢性連日性頭痛のうち2．3「慢性緊張型頭痛」は初版から採用されている．新たに4．7「持続性片側頭痛」，4．8「新規発症持続性連日性頭痛（NDPH）」が採用されたので，慢性連日性頭痛の頭痛タイプはすべて新分類でもコード化可能となった．

おわりに

新分類は，世界中の頭痛専門家の英知が結集され，約2年間の議論を経てできあがった160頁の大作で，慢性頭痛の研究・治療には必須の文献である．この新国際頭痛分類の普及と活用が切に望まれる．現在，日本頭痛学会・新国際分類普及委員会と厚労省頭痛ガイドライン研究班が共同作業で翻訳作業中である．したがって，本稿の訳語は暫定案であることをお断りしておく．頭痛分類は将来的には頭痛の遺伝子がさらに解明され，新たな分子生物学的な頭痛分類が提案される可能性を秘めていることを付言しておく．

間中信也

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雑　誌

平成 14 年度

□ CASE REPORT □

Early Diagnosis of Vertebral Dissecting Aneurysm: A Magnetic Resonance Angiography Study

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Abstract

We report a patient with dissecting aneurysm who presented with a sudden severe headache without any neurological symptoms. Although brain computed tomography (CT) scan and MRI were negative, magnetic resonance angiography (MRA) showed a pseudocavity in a segment of the left vertebral artery. In addition, the dissecting wall of the left vertebral artery was clearly visualized in the original images of MRA. Our findings indicate that brain CT, MRI or cerebral angiography alone are sometimes inadequate for the diagnosis of vertebral dissecting aneurysm, and that MRA and its original images are necessary to establish the correct diagnosis.
(Internal Medicine 41: 1193–1195, 2002)

Key words: dissection, aneurysm, vertebral artery, headache, magnetic resonance imaging, original image

Introduction

Patients with intracranial dissecting aneurysm present with a sudden severe headache associated with various neurological symptoms (1–3). The diagnosis of intracranial dissecting aneurysm is based on the demonstration of a dissecting vessel or double lumen (1, 2). In most instances, a definitive diagnosis is established by cerebral angiography but the demonstration of a dissecting vessel by magnetic resonance imaging (MRI) examination has been documented in recent years (4). However, brain computed tomography (CT) and MRI alone are not adequate for the correct diagnoses of intracranial dissecting aneurysms (1–3).

We present here a patient who presented with a sudden severe headache but without any neurological symptoms. The patient was early diagnosed as dissecting aneurysm by magnetic resonance angiography (MRA).

For editorial comment, see p 1094.

Case Report

The patient was a 55-year-old man with no clear past history. He felt a sudden severe pain in the occipital region after scuba diving on July 20, 2000, followed by nausea and vomiting. Physical examination at the outpatient clinic of the local hospital showed no paralysis or sensory disturbances and brain CT scan examination was negative. The severe headache lasted for about 3 days. As the headache, though mitigated, persisted, he visited our hospital on July 29. The general findings on the first visit were not remarkable except for mild hypertension (140/100 mmHg). In addition, there were no clear neurological abnormalities, and no findings in the follow-up brain CT scan. There was no head injury, shoulder stiffness or symptoms of infection at onset of the headache.

Generally, when we examine a patient with sudden severe headache with nausea and vomiting during effort, it is necessary to rule out cerebral aneurysm and intracranial dissecting aneurysm other than head injury and subarachnoid hemorrhage. It is known that brain MRI is useful for the diagnosis of subarachnoid hemorrhage and cerebral aneurysm. Therefore, we performed brain MR examination in this case on August 3, 2000 (using Siemens Magnetom Vision 1.5 tesla) in addition to brain CT examination. It revealed no abnormalities in the cerebral parenchyma, subarachnoid space or vertebral arteries on T2-weighted imaging (T2WI) (Fig. 1). The brain MRA (3-D time of flight; 3-D TOF) in a segment of the left vertebral artery demonstrated findings compatible with a pseudocavity (Fig. 2A). The dissecting wall of the left vertebral artery was clearly visualized in the original images of MRA for about 2 or 3 mm (Fig. 2B). After these examinations, cerebral angiography was performed, and left vertebral stenosis was observed in this case (Fig. 3). Based on these findings, he was diagnosed as a spontaneous intracranial dissecting aneurysm of the left vertebral artery. The patient was initiated on antiplatelet medi-

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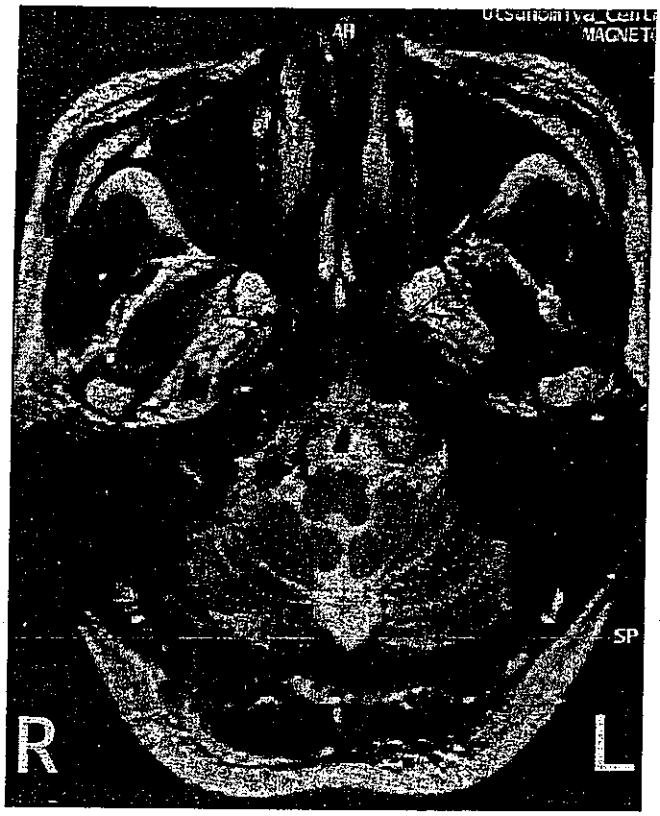

Figure 1. T2-weighted image shows no abnormality in the cerebral parenchyma, subarachnoid space or vertebral arteries (TR 4,000 ms, TE 100 ms).

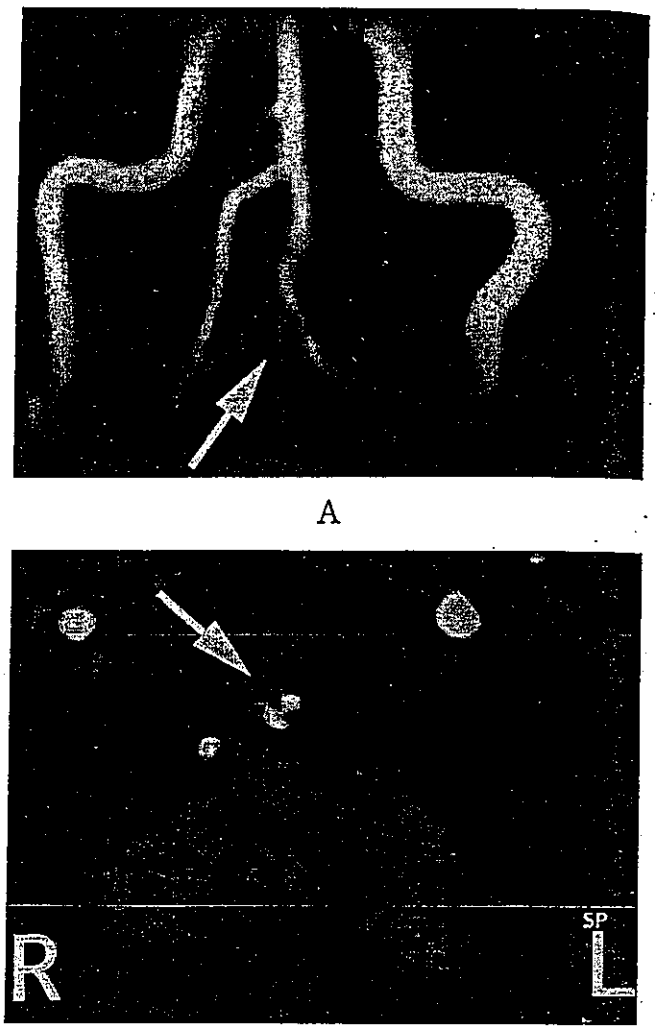

Figure 2. MRA (3-D time of flight, TR 36 ms, TE 7 ms, flip angle 20°, slice thickness 0.7 mm) shows dissection in the left vertebral artery (arrow) (A). The original image clearly shows the dissecting wall of the left vertebral artery (B).

cation to prevent complications such as cerebral infarction.

Comments

Intracranial dissecting aneurysms generally manifest suddenly at onset and often give rise to cerebrovascular disorders such as cerebral infarction in the region supplied by the injured artery or subarachnoid hemorrhage (1–3). While intracranial dissecting aneurysms underlie less than 1% of unselected brain ischemic events, they may account for 5% or more of ischemic stroke in young adults without risk factors for cerebrovascular disorders (5). Furthermore, most cases (about 89%) have clinical complications such as cerebral infarction or subarachnoid hemorrhage, however 88% of the patients with intracranial dissecting aneurysm make a good recovery (6, 7). Development of a sudden severe headache in the occipital region warrants a complete work-up to exclude dissecting aneurysm of the basilar or vertebral artery, including cerebral angiography (2, 3). However, the patient is treated with an analgesic and observed for a period of time when neurological and hematological examinations are negative in cases presenting with sudden severe headache with nausea or vomiting alone, particularly after excluding cerebral or subarachnoid hemorrhage by brain CT and cerebrospinal fluid examination. In fact, the presence of headache alone without symptoms suggestive of cerebral infarction is inadequate for the diagnosis of intracranial dissecting aneurysm and only a few studies have reported the opposite (5, 6). In the present patient, severe headache occurred suddenly, such symptoms that causes subarachnoid hemorrhage were doubted, without clear symptoms of cerebral infarction or subarachnoid hemorrhage. Furthermore, the brain CT scan was negative and MRI examination revealed no abnormality in the cerebral parenchyma and subarachnoid space, and no abnormality of the vertebral artery due to a change in the flow void was demonstrated in T2WI. However, the presence of intracranial dissecting aneurysm of the left vertebral artery was suspected when the brain MRA was performed, and

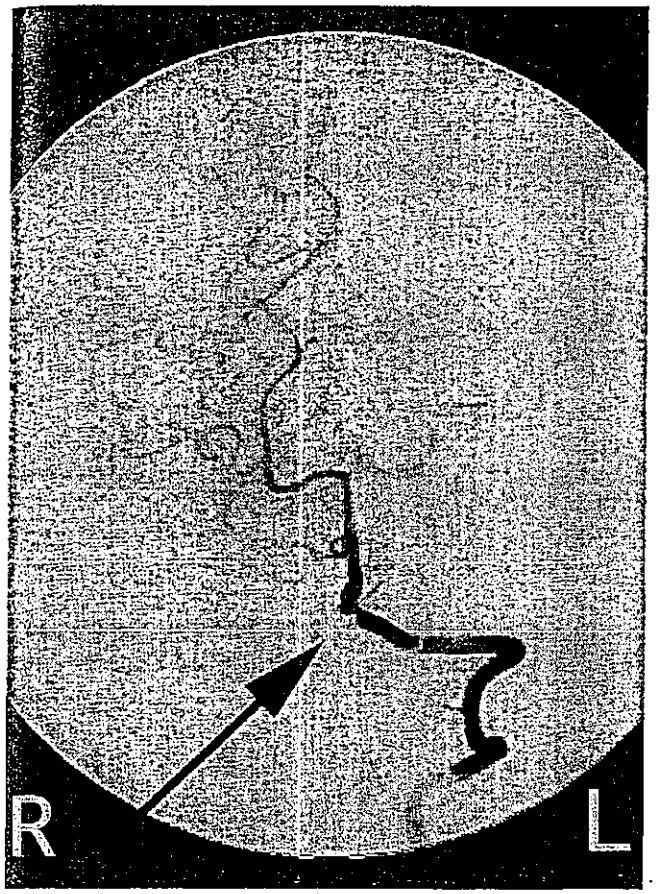

Figure 3. Cerebral angiography shows stenosis of the left vertebral artery.

a double lumen characteristic of intracranial dissecting aneurysm was clearly confirmed in the original images of MRA. MRA can be performed easily by standard MRI equipment at many institutions. The acquisition of the original images does not necessitate special skills.

Early detection of intracranial dissecting aneurysm is considered helpful for prevention of subsequent complications, such as cerebral infarction and subarachnoid hemorrhage, which is highly likely to occur (5). The results obtained in the present case indicate that brain CT and MRI alone are not adequate in some patients with sudden severe headache, such symptom that causes subarachnoid hemorrhage to be doubted, and that analysis of MRA and its original images should establish the correct diagnosis.

Summary

We described a case of intracranial dissecting aneurysm that manifested itself in sudden headache and was diagnosed early with MRA. When examining patients with the complaint of sudden severe headache with nausea and vomiting, the differential diagnosis should include subarachnoid hemorrhage and intracranial dissecting aneurysm. In addition to brain CT and MRI and cerebrospinal fluid examination, MRA and its original images should be examined to establish the correct diagnosis, especially in young individuals without risk factors for cerebrovascular disorders. Since MRI is noninvasive and can be performed easily, it is quite suitable for the identification of cerebrovascular disorders. On the other hand, MRA and its original images provide more information that could be used for the early detection of vertebral dissecting aneurysms and the prevention of complications.

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Zolmitriptan is effective and well tolerated in Japanese patients with migraine: a dose–response study

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Cephalalgia

Sakai F, Iwata M, Tashiro K, Itoyama Y, Tsuji S, Fukuuchi Y, Sobue G, Nakashima K & Morimatsu K. Zolmitriptan is effective and well tolerated in Japanese patients with migraine: a dose–response study. Cephalalgia 2002; 22:376–383. London. ISSN 0333-1024

This phase II study investigated the efficacy, tolerability and dose–response relationship of oral zolmitriptan in the treatment of a single migraine attack in Japanese patients. A bridging analysis then assessed the validity of extrapolating western clinical data to these Japanese patients. In this multicentre, randomized, double-blind, placebo-controlled study, patients received a single dose of placebo or zolmitriptan 1, 2.5 or 5 mg. The primary endpoints were 2-h headache response and the tolerability of zolmitriptan. A statistically significant dose–response relationship was observed for the 2-h headache response ($P=0.003$). The 2.5 mg group had significantly greater 2-h headache response than the placebo group ($P=0.032$). The adverse event profile was similar to that reported in western patients, and no adverse events unique to the Japanese population were observed. The bridging analysis report confirmed similar efficacy and tolerability of zolmitriptan in Japanese and western populations. In the Japanese patients, the estimated response rates were 34.3%, 45.2%, 57.7% and 66.2% for placebo, and zolmitriptan 1, 2.5 and 5 mg, respectively, while in the western population the corresponding rates were 39.9%, 49.6%, 61.2% and 71.7%. Zolmitriptan is effective and well tolerated in the acute treatment of migraine in Japanese patients. The optimal dose was 2.5 mg, although the 5 mg dose may provide further benefit for some patients. The bridging analysis supports extrapolation of data from western to Japanese patients. □ *Bridging analysis, Japanese patients, migraine, Zolmitriptan*

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Introduction

Zolmitriptan is an orally active 5-$HT_{1B/1D}$ receptor agonist widely used in the acute treatment of migraine. An extensive clinical trial programme conducted primarily in Caucasian patients in the USA and Europe has established that zolmitriptan is consistently effective and well tolerated across varying patient subgroups and migraine types (1–4). The optimal dosage of zolmitriptan in these studies was found to be 2.5 mg, with 2-h headache response rates of 62–65% and a good safety profile.

The results from the above studies were considered in the preparation of the clinical study design and plan for evaluating the efficacy and tolerability of zolmitriptan in Japanese subjects.

Data from a concurrent study demonstrated that the pharmacokinetics of zolmitriptan in Caucasian and Japanese healthy volunteers were comparable (5). Furthermore, and consistent with previous pharmacokinetic and clinical efficacy studies in Caucasian subjects, this study demonstrated that zolmitriptan 2.5 mg was well tolerated in Japanese subjects. Therefore, as no clinically relevant differences between Japanese and

Caucasian subjects have been identified to date, the possibility of using the present phase II dose–response trial as a bridging study, supporting the extrapolation of overseas clinical data to Japanese subjects, was considered.

Therefore, the objectives of this study were twofold. First, to investigate the efficacy, tolerability and dose–response of oral zolmitriptan in the acute treatment of a single migraine attack in Japanese patients. Secondly, to present the results of the bridging analysis report, directly comparing results from the Japanese population with those obtained in a similar phase II study previously conducted in a western population, and to determine whether extrapolation of western data to Japanese patients is valid.

Methods

Patients

Male and female patients aged 18–64 years, with an established diagnosis of migraine with or without aura (according to International Headache Society criteria), were included in the study. Eligible patients had an age at migraine onset of <50 years, a history of migraine symptoms for at least 1 year and experienced one to six migraine attacks per month in the 3 months prior to the study.

Exclusion criteria were: a history of basilar, ophthalmoplegic or hemiplegic migraine; non-migraine headaches reported on >10 days per month during the previous 6 months; ischaemic heart disease, dysrhythmias or cardiac accessory pathway disorders (e.g. Wolff-Parkinson–White syndrome); severe liver or renal impairment; uncontrolled hypertension; pregnancy or lactation; severe allergies or hypersensitivity to drugs; participation in a clinical study during the past 3 months; or required use of ergotamine preparations.

This study was designed and conducted in compliance with the ethical principles of good clinical practice and the Declaration of Helsinki, and all patients gave written informed consent before any study procedures were begun.

Study design and treatments

This was a randomized, placebo-controlled, double-blind, parallel-group study conducted in 81 centres throughout Japan. Participating investigators were neurologists specializing in the treatment of headache throughout Japan and all recruited a small number of patients (maximum 10), thus decreasing the potential for any centre-to-centre bias. After a screening visit to determine eligibility for the study, patients were randomized into a 1:1:1:1 ratio to receive zolmitriptan 1, 2.5 or 5 mg or placebo for the acute treatment of a single migraine attack.

Patients were requested to treat only moderate or severe migraine headaches with study medication. Before administration of the study treatment, use of other medication was restricted: acute treatment with ergotamine was not permitted within the previous 48 h, while analgesics, steroids, antidepressants, antiemetics, anticonvulsants or sedatives were not allowed in the previous 8 h. Patients could not take approved escape medication until completion of the 4-h post-dose assessment.

Assessments

Patient diary cards were used to record data on the treated migraine headache immediately before and at 0.5, 1, 2 and 4 h after administration of the study medication. The primary endpoints were the headache response rate at 2 h, defined as a reduction in migraine intensity from moderate or severe at baseline to mild or no pain, and an overall safety rating for zolmitriptan (the proportion of patients with 'no problem'). Secondary outcome measures included headache response at 0.5, 1 and 4 h, pain-free response rate (reduction from moderate or severe at baseline to no pain) at 2 h, complete response (a headache response at 2 h and then no recurrence or use of escape medication within 24 h), improvement of associated headache symptoms, the incidence of headache recurrence, use of escape medication, the patients' global impression of treatment and the tolerability profile of zolmitriptan.

Enrolment, baseline and follow-up safety evaluations included laboratory assessments, vital signs and a 12-lead electrocardiogram. All adverse events occurring between dosing and follow-up were recorded on patient diary cards and converted to WHOART adverse event classifications.

Statistical analysis

The dose–response relationship for all endpoints was tested statistically using the Cochran-Armitage trend test at the one-sided 5% significance level. Headache response rates at 2 h and use of escape medication in the zolmitriptan 2.5 mg and placebo groups were also compared directly using the chi-square test at the two-sided 5% significance level. Treatment by centre interactions had been fully tested for and not detected in several previous studies, so this aspect was not explored in the current multicentre study. Efficacy analysis was performed on the evaluable case population (common expression in Japanese studies, equivalent to per

protocol population), whereas the safety analysis was performed on the all-treated population. However, for the primary efficacy endpoint of 2-h headache response, the all-treated population was also analysed.

From the overseas data, it was assumed that 2-h headache responses of 30%, 45%, 60% and 65% could be expected in this study with placebo and zolmitriptan 1, 2.5 and 5 mg, respectively. A total of 200 evaluable patients (50 per group) would give over 90% power to detect a dose response across the four groups, using the Cochran-Armitage test (5% significance level). Moreover, at a significance level of 5%, 50 evaluable patients per group would give over 80% power to detect a significant difference between placebo and zolmitriptan 2.5 mg (the optimal dose in western populations), using a two-sided chi-squared test.

Bridging analysis

The methods for the bridging analysis report were defined prior to Key code break meeting for the Japanese dose–response study. Data re-analysis was then performed using the same statistical methods and population definitions as were used in the chosen phase II study in the Caucasian population, which had a close similarity in design (1). That study also used a randomized, double-blind, placebo-controlled design, and investigated the efficacy and tolerability of zolmitriptan 1, 2.5, 5 and 10 mg in the treatment of a single moderate or severe migraine. The primary endpoint was 2-h headache response, while secondary endpoints included safety, pain-free response, headache response at 0.5, 1 and 4 h, use of escape medication, and improvement of associated symptoms. The main differences between the two studies were that the western study also included a 10-mg dose and the optional use of a second dose. The primary endpoint for the bridging analysis was 2-h headache response.

To directly compare the two studies, two statistical approaches were used. First, a logistic regression model was fitted using dose as a categorical covariate and baseline headache intensity as a factor, allowing formal comparisons of the response rate to each dose of zolmitriptan with that of placebo, at a significance level of 5%. Secondly, a logistic regression model was fitted using dose as a continuous covariate and baseline intensity as a factor, allowing the dose–response curve across the range of doses to be estimated, at a significance level of 5%. The western study was one of the previously mentioned studies where existence of centre by treatment interactions was explored and not found, so such analyses were not repeated for the bridging analysis. Centre effects were also tested for, but found to not significantly contribute to the logistic regression models. Analyses were performed on the protocol-preferred populations of both studies. The adverse events of both studies were described in the bridging analysis report using modified COSTART terms.

Results

Patient characteristics

A total of 289 patients were randomized to treatment; of these, 58 patients were excluded because they did not take trial medication (Table 1). A further two patients were excluded because of improper acquisition of informed consent or incorrect administration of study medication. Therefore, the all-treated population consisted of 229 patients. An additional 27 patients were excluded from this group because of protocol deviations or violation of inclusion/exclusion criteria, resulting in an evaluable case population of 202 patients in which the assessment of efficacy was performed.

The demographic characteristics were similar across the four treatment groups (Table 2). Overall, 74% of patients were female and the mean age of the patient population was 38 years. The mean age at migraine onset was 23 years and the mean number of attacks per month was 3.0. The majority of patients typically experienced migraine without aura (64%) and associated symptoms of nausea (90%), vomiting (54%) and photophobia (56%). Phonophobia was experienced by 45% of patients. The majority of treated attacks were of moderate intensity (73%). The median time between onset of migraine and treatment with study medication was 2.8 h.

Efficacy

A statistically significant dose–response relationship was observed for the primary endpoint of 2-h headache

Table 1 Patient accountability

		Zolmitriptan			
	Placebo	1 mg	2.5 mg	5 mg	Total
Randomized to treatment	77	68	75	69	289
Did not take medication	17	15	14	12	58
Excluded from all analysis	1	1	0	0	2
All-treated population	59	52	61	57	229
Violated inclusion/ exclusion criteria	4	1	0	0	5
Deviated from protocol	6	4	7	5	22
Evaluable case population	49	47	54	52	202

Table 2 Demographic and baseline migraine characteristics of the evaluable case population

	Placebo ($n=49$)	Zolmitriptan 1 mg ($n=47$)	Zolmitriptan 2.5 mg ($n=54$)	Zolmitriptan 5 mg ($n=52$)
Gender *n* (%)				
Female	35 (71.4)	36 (76.6)	37 (68.5)	42 (80.8)
Male	14 (28.6)	11 (23.4)	17 (31.5)	10 (19.2)
Age (mean ± SD, yr)	37.5 ± 11.6	38.4 ± 13.1	37.6 ± 12.4	39.6 ± 12.1
Mean age at onset (years)	22.6	23.7	21.7	25.6
Mean duration of migraine *n* (%)				
0–12 h	31 (63.3)	35 (74.5)	39 (72.2)	35 (67.3)
12 and ≤24 h	8 (16.3)	5 (10.6)	5 (9.3)	9 (17.3)
24 and ≤48 h	5 (10.2)	7 (14.9)	5 (9.3)	6 (11.5)
>48 and ≤72 h	5 (10.2)	0	5 (9.3)	2 (3.8)
Type of migraine				
With aura	21 (42.9)	15 (31.9)	17 (31.5)	19 (36.5)
Without aura	28 (57.1)	32 (68.1)	37 (68.5)	33 (63.5)

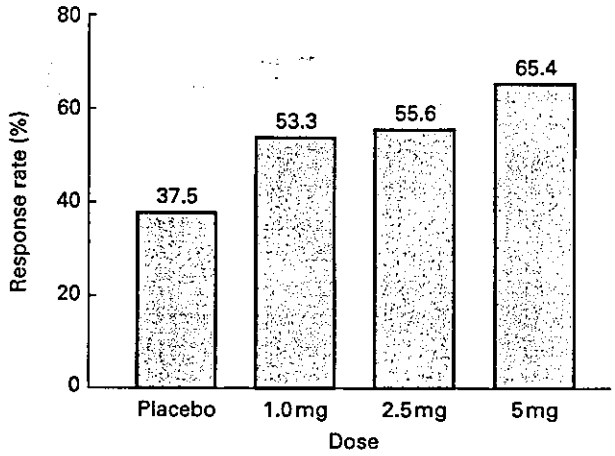

Figure 1 Headache response rates at 2 h after acute treatment of migraine with placebo or zolmitriptan 1, 2.5 or 5 mg in Japanese patients.

response. Response rates in the evaluable case population were 53.3% (95% CI 37.9% to 68.3%), 55.6% (41.4% to 69.1%) and 65.4% (50.9% to 78.0%) for zolmitriptan 1.0, 2.5 and 5.0 mg, respectively, compared with 37.5% (23.9% to 52.7%) for placebo (Cochran-Armitage test $P=0.003$; Fig. 1). Similar response rates occurred in the all-treated population: 52.0%, 54.2% and 66.7% for zolmitriptan 1.0, 2.5 and 5.0 mg, respectively, compared with 34.5% for placebo (Cochran-Armitage test $P<0.001$). Comparison of response rates for zolmitriptan 2.5 mg and placebo in the all-treated population found a statistically significant difference ($P=0.032$); in the evaluable case population this comparison did not reach significance ($P=0.068$). Comparable results were observed when 2-h headache response rates were analysed by baseline migraine characteristics (Table 3). Zolmitriptan was also similarly effective regardless of the pre-treatment migraine duration (Table 3).

Secondary endpoints

For the secondary endpoints of headache response at 0.5 and 1 h, no statistically significant dose–response relationship was found ($P=0.423$ and $P=0.283$, respectively). At 4 h, the dose–response relationship was significant ($P=0.032$), with response rates of 75.6%, 76.5% and 78.3% for zolmitriptan 1.0, 2.5 and 5.0 mg, respectively, and 61.0% for placebo (Table 4).

There was no significant dose–response relationship for the percentage of patients pain free at 2 h, although a numeric trend was evident. In addition, there was no consistent dose–response relationship for the improvement of associated symptoms, although at 4 h a significant dose–response relationship was observed for improvement in vomiting.

A significant dose–response relationship was observed for the percentage of patients experiencing a complete response at 24 h: 37.8%, 46.3% and 46.2% of patients receiving zolmitriptan 1, 2.5 or 5 mg, respectively, reported a complete response compared with 22.9% of placebo recipients ($P=0.004$; Table 4). There was a significant difference between the zolmitriptan 2.5 mg group and placebo in the use of escape medication ($P=0.041$). No significant dose–response relationship was observed for recurrence rates or for patients' impression of treatment, although a higher proportion of patients in the zolmitriptan 2.5 mg and 5 mg groups considered treatment to be 'useful' or 'very

Table 3 Number (%) of patients with a 2-h headache response according to demographic or baseline migraine characteristics

	Placebo ($n=48$)	Zolmitriptan 1 mg ($n=45$)	Zolmitriptan 2.5 mg ($n=54$)	Zolmitriptan 5 mg ($n=52$)
Gender				
Female	10/34 (29.4)	17/35 (48.6)	18/37 (51.4)	27/42 (64.3)
Male	8/14 (57.1)	7/10 (70.0)	12/17 (70.6)	7/10 (70.0)
Headache intensity				
Moderate	14/38 (36.8)	21/32 (65.6)	22/38 (57.9)	25/37 (67.6)
Severe	4/10 (40.0)	3/13 (23.1)	8/16 (50.0)	9/15 (60.0)
Aura				
Present	6/16 (37.5)	4/8 (50.0)	6/10 (60.0)	8/14 (57.1)
Absent	12/32 (37.5)	20/37 (54.1)	24/44 (54.5)	26/38 (68.4)
Pre-treatment migraine duration (h)				
≤1	5/11 (45.5)	9/12 (75.0)	7/15 (46.7)	11/17 (64.7)
1 to ≤2	0/8 (0)	4/9 (44.4)	3/8 (37.5)	4/6 (66.7)
>2 to ≤3	2/3 (66.7)	2/3 (66.7)	5/6 (83.3)	4/6 (66.7)
>3	11/26 (42.3)	9/21 (42.9)	15/25 (60.0)	15/23 (65.2)

Table 4 Percentage of patients responding on secondary endpoints

	Placebo	Zolmitriptan 1 mg	Zolmitriptan 2.5 mg	Zolmitriptan 5 mg
Headache response				
30 min	12.2%	8.5%	9.8%	13.7%
1 h	26.5%	30.4%	28.3%	32.7%
4 h	61.0%	75.6%	76.5%	78.3%
Pain free (2 h)	14.6%	17.8%	18.5%	23.1%
Complete response	22.9%	37.8%	46.3%	46.2%
Recurrence	29.5%	25.0%	15.7%	28.1%
Use of escape medication	26.5%	12.8%	5.6%*	17.3%
Patients with nausea				
Baseline	71.4%	70.2%	63.0%	69.2%
2 h	45.8%	46.7%	38.9%	35.3%
Patients with photophobia				
Baseline	46.9%	38.3%	44.4%	46.2%
2 h	22.9%	17.8%	16.7%	21.6%
Patients with phonophobia				
Baseline	28.6%	36.2%	29.6%	44.2%
2 h	14.6%	22.2%	18.5%	17.6%
Patients with vomiting				
Baseline	6.1%	12.8%	5.6%	15.4%
2 h	4.2%	4.4%	1.9%	2.0%

*$P=0.041$ vs. placebo (chi-square test).

useful' compared with placebo or zolmitriptan 1 mg (Fig. 2).

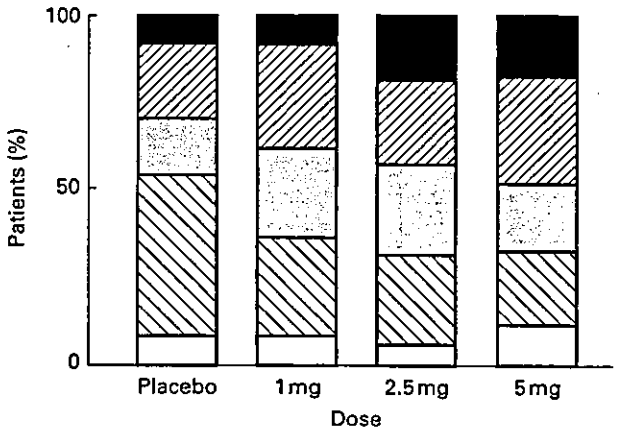

Figure 2 Patient impression of treatment after acute treatment of migraine with placebo or zolmitriptan 1, 2.5 or 5 mg in Japanese patients. ■ very useful, ▨ useful, □ no opinion, ▧ not useful, never use again.

Tolerability

Zolmitriptan was well tolerated, with the majority of patients reporting 'no problem' with respect to tolerability (79.7%, 80.8%, 68.9% and 59.6% of patients in the placebo, zolmitriptan 1, 2.5 and 5 mg groups, respectively). Adverse events were predominantly mild or moderate in intensity, and all resolved without intervention. No adverse events unique to the Japanese population were observed. The most frequently reported adverse events overall were asthenia, hyperaesthesia, aggravation of migraine, somnolence, paraesthesia and abdominal pain (Table 5). A significant dose-dependent increase in the incidence of adverse events was observed ($P<0.001$), with 13.6%, 15.4%, 32.8% and 43.9% of patients who received placebo or zolmitriptan 1, 2.5 or 5 mg, respectively, reporting at least one adverse event. No serious adverse events were reported.

An analysis of the relationship between the severity of adverse events and patient impression of treatment showed that the presence of adverse events did not affect patient ratings of the acceptability of treatment. In the zolmitriptan 5 mg group, 46.7% of patients who did not experience any adverse events assessed the treatment as 'useful' or 'very useful', compared with 56.0% of those who experienced mild or moderate events. Similarly, in the 2.5 mg dose group, 43.6% of patients with no adverse events found the treatment 'useful' or 'very useful' compared with 38.9% of those who experienced mild or moderate adverse events.

There were no clinically significant changes in laboratory values or vital signs.

Bridging analysis

Study populations for the bridging analysis were redefined according to the inclusion criteria of the phase II study in the western population, and therefore include a slightly different number of patients. The protocol-preferred populations included 191 patients from the Japanese study and 751 patients from the western study. The all-treated safety populations were 231 and 855 patients, respectively. The demographics of the two study populations were similar: in the Japanese study, 74.3% of patients were female and the mean age was 38.6 years, while in the western study, 88.1% of patients were female and the mean age was 41.2 years. The migraine histories of the two groups were also comparable in terms of attack frequency, age at onset, and the proportion of patients who did not normally experience aura. However, the average duration of untreated migraines was shorter in Japanese patients, with 70.7% reporting migraines of less than 12-h duration. In comparison, the majority of migraines (60.1%) in western patients lasted between 24 and 72 h.

Comparison of the 2-h headache response rates in the Japanese study population with those of the previously studied western population showed similar response rates and confirmed the dose–response relationship (Table 6).

Logistic regression analysis of 2-h headache response, with dose as a categorical variable and baseline intensity as a factor, found a statistically significant difference in the Japanese study between zolmitriptan 2.5 mg vs. placebo ($P=0.017$) and zolmitriptan 5 mg vs. placebo ($P=0.001$), but not for 1 mg vs. placebo ($P=0.102$). A headache response at 2 h was 2.6 (95% confidence interval: 1.2–5.8) and 4.2 (95% CI: 1.8–10.0) times more likely in patients treated with zolmitriptan 2.5 and 5 mg, respectively, than in those treated with placebo. In western patients, all three doses were significantly more effective than placebo, and patients were 2.5 (95% CI: 1.5–4.2), 4.0 (95% CI: 2.5–6.4) and 4.4 (95% CI: 2.8–7.1) times more likely to have a headache response with zolmitriptan 1, 2.5 and 5 mg, respectively, than with placebo.

Further logistic regression analyses were performed using dose as a continuous variable and baseline intensity as a factor. The derived parameter estimates are shown in Table 7. Dose–response curves were defined from the parameter estimates of these models, allowing comparisons of the dose–response curves for the two study populations. The estimated response rates showed a clear similarity between the Japanese and western populations. In the Japanese study group, estimated response rates were 34.3%, 45.2%, 57.7% and 66.2% for placebo and zolmitriptan 1, 2.5 and 5 mg, respectively, while in the western population the corresponding rates were 39.9%, 49.6%, 61.2% and 71.7% (Fig. 3). Taken together, these analyses of the primary endpoint data show that the dose–response curves in these two studies were remarkably similar; as

Table 5 Adverse events occurring in more than 5% of patients in any treatment group

		Zolmitriptan		
	Placebo ($n=59$)	1 mg ($n=52$)	2.5 mg ($n=61$)	5 mg ($n=57$)
Asthenia	1 (1.7)	1 (1.9)	1 (1.6)	4 (7.0)
Hypoaesthesia	0	1 (1.9)	1 (1.6)	4 (7.0)
Abdominal pain	1 (1.7)	0	1 (1.6)	4 (7.0)
Paraesthesia	0	0	0	3 (5.3)
Aggravation of migraine	0	2 (3.8)	2 (3.3)	3 (5.3)
Somnolence	1 (1.7)	0	2 (3.3)	3 (5.3)
Hypertension	0	0	0	3 (5.3)
Palpitation	0	0	0	3 (5.3)

Table 6 Estimated response rates using logistic regression models with quadratic trends and adjusting for baseline intensity

		Zolmitriptan		
Response rate (%)	Placebo	1 mg	2.5 mg	5 mg
Japanese population				
Severe migraine	23.4	32.8	44.9	54.0
Moderate migraine	37.0	48.3	60.9	69.2
Total	34.3	45.2	57.7	66.2
Western population				
Severe migraine	23.1	31.1	42.4	54.6
Moderate migraine	44.1	54.2	65.9	75.9
Total	39.9	49.6	61.2	71.7

Table 7 Parameter estimates of the 2-h headache response in the Japanese and western study populations using a continuous model with linear and quadratic trends

	Parameter estimate	*P*-value
Japanese study		
Linear trend	0.514	0.073
Quadratic trend	−0.049	0.368
Baseline intensity	−0.650	0.063
Western study		
Linear trend	0.438	0.0001
Quadratic trend	−0.032	0.0001
Baseline intensity	−0.964	0.0001

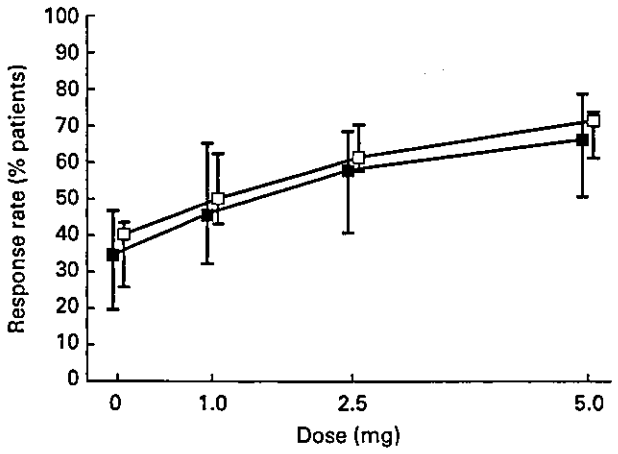

Figure 3 Estimated 2-h headache response rates (using logistic regression models with quadratric trends adjusted for baseline intensity) with 95% confidence intervals in Japanese (■) and western (□) patients.

already recognized from western data, the dose–response curve in the Japanese population demonstrated a flattening of the curve at the 2.5 mg dose. These findings related to the primary endpoint were supported by the analyses of secondary endpoints. Headache response rates at 1 and 4 h were higher in all zolmitriptan treatment groups than in the placebo group for both study populations. A clear dose–response relationship was also observed for complete response rates. In the Japanese study population, complete response rates were 19%, 41%, 47% and 54% for placebo and zolmitriptan 1, 2.5 and 5 mg, respectively, compared with rates of 17%, 30%, 40% and 45% for the western study population.

Recurrence rates were lower with all doses of zolmitriptan than with placebo, and this was consistent for both study populations. In the Japanese study, the incidence of recurrence within 24 h in patients with a response at the 2-h time point was 41%, 16%, 13% and 17% for placebo and zolmitriptan 1, 2.5 and 5 mg, respectively. Comparative rates in the western study population were 46%, 36%, 37% and 32%.

Tolerability

The profile of adverse events in the Japanese population was similar to that reported in western patients, although the overall incidences were somewhat lower in the Japanese patients (24% vs. 39%). This difference was observed for all doses, including placebo, suggesting that this is more likely to be a cultural effect rather than being treatment related. The type of adverse events reported was similar in the two study populations, with the most common events in Japanese patients being asthenia (4.1%), paraesthesia (3.5%), aggravation reaction (3.5%), somnolence (2.9%), and vomiting (2.9%), while in the western study the most frequent events were dizziness (8.1%), paraesthesia (7.0%), somnolence (6.1%), nausea (5.6%), warm sensation (4.3%) and asthenia (2.9%). In both studies, the majority of adverse events were mild or moderate in intensity.

Discussion

This phase II dose–response study demonstrates that oral zolmitriptan is effective in the acute treatment of migraine in Japanese patients. A significant dose–response relationship was observed for the primary endpoint of 2-h headache response, and the results indicated that 2.5 mg is the minimally effective dose. Although the comparison of the 2-h headache response between zolmitriptan 2.5 mg and placebo showed no statistically significant difference in the evaluable case population, a significant difference was observed in the all-treated population. One possible reason for the lack of significance observed in the evaluable case population was that more patients in the zolmitriptan group treated a migraine of severe intensity compared with the placebo group (29.6% vs. 20.4%). Baseline migraine intensity is a well-known prognostic factor for headache response, and therefore this imbalance in the distribution of baseline intensity may have prevented the detection of a statistically significant difference. This is supported by the finding of the bridging analysis report, where analyses of these study results adjusted for baseline intensity and demonstrated a significant difference between zolmitriptan 2.5 mg and placebo.

The bridging analysis was performed to directly compare the efficacy and tolerability data obtained in the Japanese patients with those from a previous phase II study conducted in a western population,

and thereby to determine whether extrapolation of western data into Japanese patients is valid. The bridging analysis of the efficacy data from the two studies shows that zolmitriptan is similarly effective in Japanese and western populations. As highlighted above, the bridging analysis provided baseline-adjusted estimated response rates and these showed that 2-h response rates to zolmitriptan 2.5 mg were 57.7% and 61.2% in the Japanese and western populations, and with zolmitriptan 5 mg were 66.2% and 71.7%, respectively. In both populations, the 2.5 mg dose was clearly more effective in the treatment of migraine and associated symptoms compared with placebo and the 1 mg dose, while the 5.0 mg dose provided small but consistent improvements over the 2.5 mg dose.

Zolmitriptan was well tolerated in Japanese patients, and the profile of reported adverse events was similar to those previously reported with zolmitriptan in mainly Caucasian populations (6). No adverse events unique to the Japanese population were observed. Direct comparison with a western population in the bridging analysis confirmed that the nature of adverse events was similar in the two studies, although a smaller proportion of patients in the Japanese study experienced adverse events (24% vs. 39%). Interestingly, this lower incidence of adverse events was observed even though it has previously been shown that the AUC and C_{max} of zolmitriptan are approximately 20% higher in Japanese subjects (5). Therefore, the data obtained in the present study confirm assumptions that although Japanese subjects have a somewhat higher exposure to zolmitriptan, this will not be associated with clinically relevant differences in efficacy or tolerability. The incidence of adverse events was dose-dependent, with a marginal increase in the frequency of adverse events in the 5 mg dose group.

In conclusion, the results from this dose–response study and from the bridging analysis show that oral zolmitriptan is effective and well tolerated in the Japanese population. Balancing both efficacy and tolerability, 2.5 mg was considered to be the optimal dose, as is also recommended for western populations, although the 5 mg dose may provide further benefit for some patients. The similar efficacy and tolerability of zolmitriptan observed in the bridging analysis of Japanese and western study data support the extrapolation of western clinical data to Japanese patients.

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Interferon β-1a treatment of corticosteroid sensitive polymyositis

Inflammatory myopathies may occur with malignancies or collagenosis (lupus erythematosus, rheumatoid arthritis, overlap syndrome, or mixed connective tissue disease) or be associated with retroviral disease.[1] Idiopathic inflammatory myopathies may present as dermatomyositis, inclusion body myositis, or polymyositis.

Most patients with polymyositis respond well to pulse treatment with corticosteroids. However, this treatment is usually restricted to short periods of time in an effort to contain severe bouts of the disease. A more chronic term of corticosteroid treatment is often desirable but this approach is complicated by untoward side effects and by the tolerability of the patient. Most authors recommend a combination of azathioprine and low doses of corticosteroids. If this regimen fails, ciclosporin A, immunoglobulins, or cyclophosphamide is recommended.[2] β Interferons are a new group of immunomodulatory drugs widely used for treatment of patients with multiple sclerosis, a disease of probable autoimmune origin.[3] However, no data are available on the efficacy of β interferons in the treatment of other autoimmune diseases.

Here we report the results of treatment of a patient with a longstanding history of polymyositis with interferon β-1a.

At the age of 15 years, the female patient noticed leg weakness associated with muscular pain in her calves during physical exercise. Laboratory investigation found a serum creatine kinase (CK) concentration of 9000 U/l. Necrotising myositis was diagnosed based on muscle biopsy and corticosteroid treatment was initiated. This treatment was initially well tolerated and the symptoms resolved. Attempts to discontinue the corticosteroid treatment led to recurrent exacerbations of the disease. Treatment was therefore initiated with second and third line immunosuppressant and immunomodulatory drugs (azathioprine, ciclosporin A, intravenous immunoglobulins, methotrexate) in an attempt to contain disease activity and to taper corticosteroids below the cushing level. When the patient developed spontaneous fractures, all treatment was halted; however, the patient continued to deteriorate clinically. Thus, cyclophosphamide pulse therapy in combination with corticosteroid treatment was initiated. Although each pulse reduced the serum CK from approximately 3000 U/l to 1000 U/l, the reduction was not sustained. During the course of the disease, two hospitals performed biopsies 3 and 11 years after the onset of symptoms. Both biopsies confirmed the diagnosis of polymyositis that showed a mixed lymphocytic, monocytic, and mononuclear infiltrate. No sign of a storage disease or inclusion body myositis could be detected. At the age of 32 years, 17 years after the onset of symptoms, she was referred to our hospital.

On admission the patient was able to walk a maximum of 50 m with the help of aids, climb two steps, and stand with straightened knees. Longer distances required the use of a wheelchair. Physical examination showed proximal accentuated weakness of the limbs with predominant involvement of both legs. The deep tendon reflexes were reduced in the upper extremities and absent in the lower ones. The remaining physical examination was unremarkable. The patient refused additional diagnostic procedures including a rebiopsy and electromyography.

The patient was administered 22 μg of interferon β-1a subcutaneously (Rebif®, Serono, Geneva, Switzerland) every other day. She tolerated the treatment well and steroid treatment was stopped permanently. After three and a half years of follow up with interferon β-1a treatment, CK concentration has stabilised at 600–1000 U/l and her severe symptoms have abated substantially. At her last visit, the patient was no longer confined to a wheelchair, walked inside her apartment without aid, and could climb one set of stairs. For longer distances she was still dependent on two walking aids.

This is, to the best of our knowledge, the first report of interferon β-1a treatment in polymyositis. Interferon β-1a treatment was initiated because it was a course of action that had not been tested before and other conventional immunosuppressive treatments proved ineffective or caused unacceptable side effects in this patient. Steroid treatment could be discontinued shortly after treatment with interferon β-1a was started. Moreover, disease activity was controlled for three years without requiring corticosteroid treatment, suggesting that beta interferons have utility in patients who require long term treatment of the disease. Since the interferon β-1a treatment has never been stopped, we can not formally exclude the possibility that the improvement reflects the natural history of the disease. However, we believe this to be highly unlikely given the longstanding history of the disease in this patient. Controlled clinical trials are necessary to fully test the efficacy of interferon β-1a in the treatment of inflammatory myopathies. Indeed, one multicentre trial with interferon β-1a is underway.[4] This case study thus suggests that interferon β-1a may be a new therapeutic option in autoimmune diseases beyond multiple sclerosis, particularly in cases where established steroid regimens fail.

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Japanese cases of familial hemiplegic migraine with cerebellar ataxia carrying a T666M mutation in the CACNA1A gene

Familial hemiplegic migraine (FHM) is an autosomal dominantly inherited disorder characterised by migraine attacks preceded by transient hemiparesis. In 1993, Joutel *et al* mapped the locus for FHM to chromosome 19p13 by linkage analysis,[1] and the causative gene was subsequently identified as the CACNA1A gene, encoding a P/Q-type calcium channel α1A subunit. Cases involving the CACNA1A gene have been found in approximately 50% of FHM cases, and linkage to chromosome 1 has been shown in some of the other families.

FHM with progressive cerebellar ataxia (FHM/PCA) has been described only in cases carrying CACNA1A mutations. Other clinical phenotypes associated with ataxia may also be caused by mutations in the CACNA1A gene, which include episodic ataxia type 2 (EA-2) and spinocerebellar ataxia type 6 (SCA6). EA-2 is characterised by recurrent episodes of attacks of cerebellar ataxia accompanied by interictal nystagmus. In SCA6, expansion of a CAG trinucleotide repeat coding for a polyglutamine stretch at the carboxyl terminus of the CACNA1A has been identified as the causative mutation.

These data suggest that mutations in the CACNA1A gene can lead to a broad spectrum of clinical presentations, and the relation

between clinical phenotypes and genotypes in FHM has been discussed in recent reports.[2–5] Here we describe a Japanese family with FHM/PCA, and discuss implications for genotype–phenotype correlations.

Case 1

A 67 year old woman was admitted to our hospital in 1995 for evaluation of cerebellar ataxia. She was born to first cousin parents. At age 30, she had an episode of unconsciousness for three days. She had suffered from reversible hemiparesis followed by throbbing migraine headaches lasting for several hours since she was 47. The hemiplegic episodes recurred often until the age of 52 years but gradually improved in frequency and severity without any treatment. She had begun to experience difficulty in walking since the age of about 62 years, and her gait difficulty had gradually progressed.

On neurological examination at the age of 67 years, she had horizontal gaze nystagmus and mild dysarthria. Her gait was ataxic, and she could stand on one foot only for a few seconds. Her tandem gait was unstable. Mild limb ataxia was also noted. Her muscle power was normal. No abnormal findings were noted in her sensory or autonomic nervous system. Her complete blood count, electrolytes, serum creatinine, and glucose levels were normal. Cerebrospinal fluid protein and sugar levels were normal. Brain magnetic resonance imaging (MRI) showed marked cerebellar vermian atrophy, but no areas of abnormal intensity were detected (fig 1). Single photon emission computed tomography (SPECT) showed low perfusion of the cerebellum. During her hospital admission, a throbbing headache followed by the sudden onset of numbness and dysaesthesia of the left upper limb were recorded.

Case 2

A 63 year old woman, a younger sister of case 1, had slight difficulty in speaking since the age of 36. Dysarthria, truncal ataxia, limb incoordination, and gaze nystagmus were noted by a neurologist at that time, and she was diagnosed as having spinocerebellar degeneration (autosomal dominant spinocerebellar ataxia presenting with pure cerebellar ataxia). At the age of 40, she had an episode of unconsciousness lasting two days (details unknown). She began to show a staggering gait at the same age. She had been suffering from reversible hemiparesis followed by throbbing migraine headaches since the age of 55. Neurological examination revealed horizontal gaze nystagmus, mild dysarthria, and mild truncal and limb incoordination, similar to those of her elder sister. The presence of cerebellar atrophy was confirmed by MRI (data not shown).

Case 3

A 37 year old man, a son of case 2, had had progressive gait and speech disturbances since childhood. He had never had migraine headache episodes. Neurological examination showed limb and truncal ataxia, nystagmus, scanning speech, hyperreflexia, and neck dystonia. MRI revealed cerebellar atrophy, particularly in the vermis.

Genetic features

Mutational analyses of the CACNA1A gene were performed in cases 1 and 2 by direct nucleotide sequence analysis of exons 4, 16, 17, and 36, in which the first four missense mutations—namely, R192Q, T666M, V714A and I1811L—were reported.[6] The analysis was performed using an ABI377 automated sequencer with cycle sequencing. A C→T transition (T666M) in the CACNA1A gene was identified in both case 1 and case 2. The number of CAG repeat units of the CACNA1A gene of case 1 was 11/11. As molecular diagnosis was performed only in cases 1 and 2, there remains the possibility of a phenocopy in case 3.

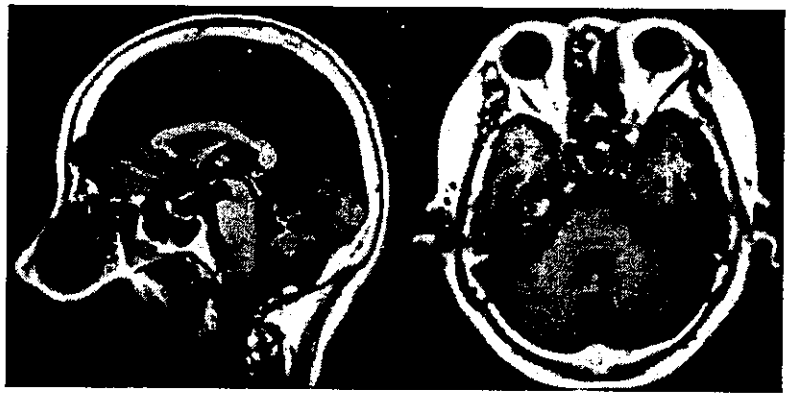

Figure 1 T1 weighted magnetic resonance imaging showing marked atrophy of the cerebellar vermis.

Comment

Although FHM cases confirmed by DNA analyses have been reported in the USA, the United Kingdom, Italy, France, Netherlands, and Denmark, this is the first report confirming the mutation in the CACNA1A gene in FHM cases in Japan. Compared with other FHM cases associated with cerebellar ataxia, characteristic clinical features of the cases of the two sisters are that migraine attacks began in their fifth decade, and that the younger sister had shown only cerebellar ataxia for more than 10 years before her first migraine attack.

The findings in our patients emphasise that the clinical presentation of FHM/PCA is more varied than previously described and that even the same mutation can lead to considerably different clinical presentations, suggesting that other genetic or environmental factors may modify the phenotype.

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Cellular schwannoma of the posterior fossa

Schwannomas are slowly growing, non-invasive neoplasms derived from Schwann cells and usually arise from peripheral nerves.[1] They may also arise from cranial nerves, most commonly the vestibular part of the VIIIth nerve. In this situation, they are sometimes associated with neurofibromatosis type 2 (NF2). The cellular variety of schwannoma has been described as a distinct "pseudosarcomatous" entity, composed of hypercellular areas of spindle shaped cells that can easily be mistaken for a malignant tumour.[2] There are fewer than 60 reported cases of intraparenchymal schwannoma[3] in which the tumour is not associated with any cranial or peripheral nerves.

In 1991, a 37 year old woman presented with left sided facial pain and numbness of several weeks' duration, accompanied by blurring of vision in her left eye. Computed tomography revealed a left trigeminal schwannoma. This was resected and, macroscopically, the tumour appeared to have been completely removed. Histology showed a schwannoma of normal cellularity with some areas composed of compact spindle cells arranged in short bundles and other areas with cells set in a loosely textured matrix containing some large, irregular vessels. There were only occasional mitotic figures and the tumour showed diffuse positivity for S100. She developed a recurrence in 1994 and underwent a further, presumed complete, resection. However, a remnant was discovered in 1995 and treated with stereotactic radiosurgery. She was followed up with regular cranial magnetic resonance (MR) scanning and a scan in March 1998 appeared satisfactory, with minimal further tumour growth and no tumour elsewhere in her brain (fig 1A).

She presented eight months later (now aged 44 years) with a two month history of increasing posterior and right sided neck pain. She also complained of headaches but had no other features of raised intracranial pressure. Examination was unremarkable except for the longstanding left trigeminal

免疫グロブリン大量静注療法に伴う頭痛の検討

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〔要約〕 免疫グロブリン大量静注（以下，IVIg）療法は，近年，免疫性神経筋疾患の治療法の一つとして頻用されており，その副作用として，ショック，過敏症，腎障害，血栓症などとともに頭痛が知られている．当科で同療法を施行された26例中8例（31%）で頭痛が認められ，うち6例は，点滴中あるいは終了直後より発現する軽度の頭痛であった．一方，発熱や悪心・嘔吐を伴う中等～高度の頭痛を呈した症例が2例あり，IVIg前後で，髄液検査にて単核球優位の細胞数増加が確認されており，無菌性髄膜炎を発症したと考えられた．いずれの症例も，頭痛の程度にかかわらず消炎鎮痛剤によく反応し経過は良好であった．IVIg療法による頭痛は，若年者および女性に発現しやすい傾向がみられた．また，血中の好酸球やIgG濃度の増加を認めたことから，IVIgによる頭痛の発現に，アレルギー的機序による無菌性髄膜炎や血液粘稠度の亢進などの関与が考えられた．

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Key Words : high-dose intravenous immunoglobulin therapy, headache, aseptic meningitis, serum hyperviscosity

はじめに

免疫グロブリン大量静注（以下，IVIg）療法は，血清自己抗体が関与する免疫性神経筋疾患に有効な治療法として近年確立され，神経内科領域で使用される頻度が年々増えている．投与方法は，通常400mg/体重kg/日の点滴静注を3～5日間で1クールとして施行する．一般に，川崎病や特発性血小板減少性紫斑病などに適応とされているが，神経筋疾患では，現在，Guillain-Barré症候群Guillain-Barré syndrome（GBS），慢性炎症性脱髄性多発ニューロパチー chronic inflammatory demyelinating polyneuropathy（CIDP）および多巣性運動ニューロパチー multifocal motor neuropathy（MMN）で保険適応となっている．IVIgの作用機序として，抗idiotype抗体による自己抗体の活性抑制，IgGの異化作用の亢進など種々の免疫作用が考えられている[1]．副作用としては，軽症のものとして，頭痛，筋痛，発熱，発疹など，また，重度のものとして，ショック，無菌性髄膜炎，脳血管障害，急性腎不全などが知られている[2]．本研究では，IVIg療法に関連して生ずる頭痛について検討を行った．

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対象・方法

対象とした症例は，当科で過去5年（1997年1月～2001年12月）の間にIVIg療法を施行した男性11例，女性15例の合計26例で，平均年齢は46.3±15.1歳であった．疾患内訳は，GBS6例，CIDP5例，MMN5例，Miller Fisher症候群2例，多発性硬化症2例，他6例

(重症筋無力症，多発筋炎，脳幹脳炎ほか)．各症例の診療録より，IVIg療法施行に伴う頭痛について，その出現頻度，頭痛の程度，発現時期，経過，その他，IVIg前後の検査結果（血液検査，髄液検査）などにつき情報を収集し，検討を行った．

結　果

IVIg療法施行中あるいは施行後に頭痛を訴えた例は，26例中8例（31%）に認められた．このうち，男性では11例中2例（18%）に頭痛が出現したのに対し，女性では15例中6例（40%）と，やや女性に多い傾向がみられた．また，頭痛の出現した症例の平均年齢が男性35.5歳，女性37.5歳であったのに対し，出現しなかった症例では，男性54.5歳，女性50.8歳と，若年ほど頭痛が出現しやすい傾向が認められた．

頭痛を発症した症例の臨床所見および検査所見を**Table 1**と**Table 2**に示す．原疾患としては，MMN 3例，CIDP 2例，他Miller Fisher症候群，GBSおよび脳幹脳炎が各1例で，合併症としては，いずれも軽度のものであったが，貧血，糖尿病，高血圧，アトピーが各1例ずつみられ，また，生活歴として経口避妊薬服用中が1例あった．投与回数に対する頭痛の発現回数であるが，6クールあるいは4クール中，4クールと比較的高頻度に発症する例もあれば，10クール以上施行しても1度しか発症しない症例もあった．頭痛の発現時期であるが，頭痛が発現した14クール中，投与開始1日目の発現が1例，2日目：2例，3日目：6例，4日目：4例，5日目：1例という結果で，3～4日目に発症しやすい傾向が認められた．頭痛の程度は，8例中6例が，点滴中あるいは終了直後より発現する軽度の頭痛で，数時間持続して自然に消失あるいは消炎鎮痛剤の頓用にて軽快した．頭痛の性状としては，軽度の頭痛例では「頭重感」の訴えが多く，高度の頭痛例で「ズキズキする，ガンガンする」といった拍動性の頭痛が1例に認められた．中等度から高度の頭痛を認めた症例1と症例2では，嘔気あるいは発熱，項部硬直などの髄膜刺激症状を伴った．IVIg療法前後で髄液検査を施行し得た3症例（症例1，2，3）において，いずれもIVIg療法後に単核球優位の細胞数の軽度増加が確認された．これら3症例も鎮痛剤の頓用にて頭痛は速やかに改善し，経過は良好であった．血液検査では，頭痛を発症した症例において，**Table 2**に示すように，IVIg療法後に末梢血好酸球およびIgG濃度の増加が比較的高頻度認められたが，その他，特記すべき所見は認められなかった．

代表として，症例1の経過を呈示する．23歳男性．両下肢のしびれを主訴に1994年に当科に来院し，CIDPの診断のもとIVIg療法をまず2クール施行された．このとき，1クール目の2～4日目に高度の後頭部痛を訴えたが，鎮痛剤の頓用のみで改善した．2クール目は頭痛はみられなかった．その後，CIDPによる右横隔神経麻痺をきたし，2001年5月よりIVIg療法を毎月1クール，総計6クール施行している．このうち3クール目の3～4日目に嘔気を伴う高度の頭痛が出現したが，このときも鎮痛剤の頓用のみで軽快している．4クール目は頭痛はなく，5および6クール目では，ともに3日目より軽度から中等度の頭痛が出現した．**Table 3**に，高度の頭痛の訴えのあった1クール目と3クール目のIVIg療法前後の髄液所見の推移を示すが，ともにIVIg療法後に細胞数の増加を認めている．なお，6クールとも免疫グロブリン投与量に差はなく，点滴速度と頭痛の発現にも明らかな関連はみられなかった．

考　察

IVIg療法に伴う頭痛は，その発現時期で大きく二つに分けられる．一つは，点滴中より出現するもので，アナフィラキシー様反応によるものと考えられており，頻度は4.7～80.0%と報告により幅がある[2,3]．しばしば，発熱，発疹，筋痛などを伴う．治療は，点滴速度を落とす，あるいは，消炎鎮痛剤・抗ヒスタミン薬の投与で速やかに症状は改善する．当科症例の大部分は，これに相当すると思われる．もう一つは，点滴終了数時間から数日後より出現する頭痛で，その原因として，無菌性髄膜炎の発症を示唆する報告が散見される[3-5]．本研究では，症例1および症例2において，比較的高度な頭痛が発現し，髄膜刺激症状を伴い，また，IVIg療法前後で，髄液検査にて軽度であるが単核球優位の細胞数増加が確認され，無菌性髄膜炎を発症したものと考えられた．なお，症例3では頭痛の程度は軽度であったが，発熱を伴い，IVIg後に髄液細胞数および蛋白の増加が認められており，同じく無菌性髄膜炎とみなされる．IVIg療法によって無菌性髄膜炎が発症する頻度についてであるが，Sekulら[4]の報告では54例中6例（11%）に発症しており，当科症例も26例中3例（11%）と同頻度で，比較的高頻度に認められた．その特徴として，点滴開始3日目から終了翌日までに高度の頭痛で発症するが，消炎鎮痛剤に比較的よく反応し，通常3～5日で改善し経過良好という傾向がみられた．IVIg療法による髄膜炎発症の機序については，まだ明らかにされていないが，IVIg療法後に末梢血および髄液中の好酸球の増加を認める症例があることから，その他の薬剤誘発性髄膜炎[6,7]と同様のアレルギー的機序が想定されている[3-5]．本研究症例においても，IVIg前後で末梢血好酸球増加