# Atypical Presentation of Aneurysmal Subarachnoid Hemorrhage: Incidence and Clinical Importance.

（脳動脈瘤性くも膜下出血の非典型発症：発症頻度と臨床的重要性）

申請者　　弘前大学大学院医学系研究科

脳神経科学領域分子神経科学分野　脳循環制御学

氏名　　小笠原　ゆかり

指導教授　大熊洋揮

## Abstract

***Background:*** The symptoms of sudden, severe headache and/or diminished consciousness typically characterize the onset of aneurysmal subarachnoid hemorrhage (SAH). However, several studies have suggested that some patients show an atypical presentation at the time of onset of SAH: symptoms lacking sudden headache and diminished consciousness. The aim of this study was to investigate incidences and clinical features of cases with atypical onset.

***Methods:*** Retrospective observational study based on data collected prospectively from all patients admitted to our hospital with SAH during the past 11years was performed. Cases with sudden headache at the time of onset were classified as the headache onset group, and cases with onset symptoms other than headache were classified as the atypical onset group. The clinical parameters were compared between the 2 groups.

***Results:*** Out of 368 SAH patients, 75 patients (20.4%) showed diminished consciousness from onset to admission, 279 cases (75.8%) were the headache onset group, and 14 patients (3.8%) were the atypical onset group. The main, initial symptoms

in the atypical onset group were nausea/vomiting, vertigo/dizziness, or neck pain/back pain. The rate of misdiagnosis of SAH upon initial medical evaluation and the rate of rebleeding after misdiagnosis were statistically significantly higher in the atypical onset group ($p=0.045$ and $p=0.043$ respectively). The Interval from onset to diagnosis was longer in the atypical onset group ($p=0.033$). The atypical onset group demonstrated a more severe clinical grade on admission ($p=0.009$), the lower rate of ruptured aneurysm repair ($p<0.001$), and the poorer outcome ($p=0.003$).

***Conclusions:*** Atypical onset is rare but has great impact on the clinical course through rebleeding exacerbated by misdiagnosis or delayed diagnosis, resulting in poor outcome.

**Key words**: subarachnoid hemorrhage, cerebral aneurysm, headache, misdiagnosis, rebleeding

## Introduction

The onset of aneurysmal subarachnoid hemorrhage (SAH) is characterized by the symptom of a sudden, severe headache. However, misdiagnosis or delayed diagnosis often occurs, because the type of headache due to aneurysmal SAH is variable.[1-5] Misdiagnosis of SAH is associated with increased risk of rebleeding and deteriorated conditions, resulting in poor outcomes.[2,6-8] Many reports have emphasized the importance of recognizing such headaches. Primary care physicians and emergency medicine doctors have recently been extensively informed on this and it may be the reason for a recent decrease in the rate of misdiagnosis.[7,9,10]

Thus, in order to achieve a further decrease in the misdiagnosis of SAH, attention should be paid to a type of presentation other than headache, because some reports have suggested the existence of cases with atypical symptoms at onset and their contribution to the misdiagnosis of SAH.[11-14] However, investigations focusing on cases presenting without headache have rarely been carried out.[15] Thus, the aim of this study was to investigate the incidence and clinical features of cases of SAH with atypical presentation.

## Materials and Methods

### *Patients*

We conducted a retrospective observational study based on data collected prospectively from all patients admitted to our hospital with SAH during the past 11years. A system by which detailed, thorough clinical histories including initial symptoms before admission to our institution were taken and recorded in the medical records has been established at our institution since 1996. This was implemented because the importance of recognizing a specific warning sign was mentioned in the guidelines for the management of SAH, as published in 1994.[16] After introducing and establishing this system, patients with aneurysmal SAH admitted to our hospital during an 11-year period between January 1, 1998 and December 31, 2008 were eligible for this study. The study was approved by our internal institutional Review Board. The clinical histories prior to admission were taken from patients, relatives or accompanying persons, primary care physicians, and emergency medicine doctors. SAH was detected by computed tomographic (CT) scan, magnetic resonance image, or lumbar puncture, and cerebral aneurysm, considered as causing SAH, was detected by digital subtraction angiography

or 3-dimentional CT angiography.

***Subtype of Patients***

According to clinical histories before admission, patients were divided into 3 groups. The cases whose clinical histories at onset were unclear because of diminished consciousness at onset through to admission were classified as the consciousness disturbance group. The cases whose clinical histories at onset could be fully obtained were divided into 2 groups: cases whose initial symptom was a sudden headache were classified as the headache onset group, and cases whose initial symptoms were symptoms other than headache were classified as the atypical onset group.

***Comparison of clinical parameters***

Clinical parameters prior to admission were compared between the headache onset group and the atypical onset group. The consciousness disturbance group was excluded from this comparative evaluation, because some of the clinical parameters before admission were unclear in the consciousness disturbance group.

As clinical parameters before admission, the interval from onset to the initial visit to medical care, the rate of misdiagnosis upon initial medical care, the interval from onset

to diagnosis by CT scan, and the rate of rebleeding were evaluated.

Unusual sudden headache with loss of consciousness or sudden deterioration of consciousness level occurring after the initial symptoms were considered the evidence of rebleeding, after other causes, such as epileptic seizure, were excluded judging from the clinical course.[17,18] In addition to the total rate of rebleeding before admission, the rate of rebleeding before visiting initial medical care, that after misdiagnosis upon the initial medical evaluation, and that after diagnosis were evaluated. In addition to the total rate of misdiagnosis upon initial medical care, the rate of misdiagnosis was calculated by subtracting the number of cases suffering rebleeding before the initial visit to medical care from the parent population; these cases could not be misdiagnosed, due to depressed consciousness resulting from the rebleeding.

As clinical parameters upon and after admission to our institutions, the clinical grade on admission was evaluated by the Hunt and Hess grade, the SAH grade on CT was assessed by Fisher's classification, and outcome was evaluated by the Glasgow outcome scale (GOS). Operability was assessed by the rate of repair of ruptured cerebral aneurysm; its general indications were Hunt and Hess grade I – IV in the

patients < 75 years old and Hunt and Hess grade I – III in the patients ≥ 75 years old, and the patients ≥ 75 years old with Hunt and Hess grade IV were basically the candidates for the delayed operation.

***Statistical analysis***

Comparisons of nonparametric data, such as the Hunt and Hess grade, Fisher group, GOS score, sites of aneurysms, interval from onset to initial visit to medical care, and interval from onset to diagnosis by CT scan were performed with the Mann-Whitney U test. Comparisons of rate of each initial symptom, rate of rebleeding, rate of misdiagnosis, and rate of operability were carried out using the chi-square test. Age between the 2 groups was compared with F-test. A p-value of less than 0.05 was considered a significant difference.

## Results

***Incidence and symptoms of atypical onset***

For 11 years, 368 aneurysmal SAH patients were admitted to our hospital. Out of the 368 patients, 75 (20.4%) were classified in the consciousness disturbance group, 279

(75.8%) were classified in the headache onset group, and 14 (3.8%) were classified in the atypical onset group (Table1, Figure 1).

The main initial symptoms in the atypical onset group were nausea/vomiting, vertigo/dizziness, or neck pain/back pain (Table1). The mean ± SD of systolic arterial blood pressure of 9 cases in the atypical onset group measured at the initial medical care was 162 ± 26 mmHg.

***Comparison of clinical parameters before neurosurgical management***

Interval from onset to initial visit to medical care showed no statistically significant difference between the headache onset group and the atypical onset group (p= 0.501) (Figure 2), although the number of cases visiting initial medical care within 3 hours after onset was greater in the headache onset group than in the atypical onset group.

Total rate of misdiagnosis of SAH in the atypical onset group was twice that of the headache onset group, without a statistically significant difference (p = 0.125) (Table 2). The number of cases suffering rebleeding before the initial visit to medical care was 17 in the headache onset group and 3 in the atypical onset group. When these cases were excluded from the parent population, because they could not be misdiagnosed due to

diminished consciousness from rebleeding, the rate of misdiagnosis was statistically significantly higher in the atypical onset group ($p = 0.045$) (Table 2).

Interval from onset to diagnosis by CT scan was statistically significantly longer in the atypical onset group ($p = 0.033$, Mann-Whitney U test) (Figure 3).

Rebleeding before the initial visit to medical care showed no statistically significant difference between the 2 groups ($p=0.065$) (Table 2). When rebleeding after misdiagnosis upon initial medical care was calculated by excluding those cases suffering rebleeding before the initial visit to medical care from the parent population, the rate of rebleeding was statistically significantly greater in the atypical onset group ($p=0.043$) (Table 2). Rebleeding after a diagnosis by CT scan and before admission to our institution showed no statistically significant difference between the 2 groups ($p=0.233$) (Table 2). Total rebleeding before admission to our institution was statistically significantly greater in the atypical onset group ($p<0.001$) (Table 2).

***Comparison of clinical parameters on admission to the neurosurgical institution***

Cases with severe clinical grade, as evaluated by the Hunt and Hess grading system, were statistically significantly greater in the atypical onset group ($p=0.009$) (Table 3). In

7 cases with grade 4 or 5 in the atypical onset group, 6 cases had suffered rebleeding before diagnosis by CT scan.

The SAH grade on CT scan showed no statistically significant difference between the 2 groups (p=0.262), although Fisher group 4 in the atypical onset group was twice that in the headache onset group (Table 3). Four cases out of 5 with Fisher group 4 in the atypical onset group had suffered rebleeding before a CT scan was performed.

The site of aneurysm causing SAH showed no statistically significant difference between the 2 groups (p=0.150) (Table 3).

***Comparison of clinical parameters after neurosurgical management***

The rate of operability was significantly lower in the atypical onset group (p<0.001) (Table 3). The reasons why repair of aneurysm was not performed in 3 cases out of 6 of the atypical onset group were severe clinical conditions due to rebleeding before admission.

Outcome evaluated by GOS score was statistically significantly poorer in the atypical onset group than in the headache onset group (p=0.003) (Table 3). The causes of poor outcomes in 6 cases out of 8 were related to misdiagnosis and delayed diagnosis.

## Discussion

A sudden, severe headache is the most typical and representative symptom at the time of onset of SAH. In cooperative studies of aneurysmal SAH in which surgery and its timing were investigated, Graf CJ and Nibbelink DW reported that 8% of 228 patients who were admitted and evaluated within 7 days after onset were symptom-free,[19] and Kassell NF, et al. reported that 10% of 3521 patients who were admitted within 3 days after SAH had no headache.[20] Recently, Naganuma M, et al. investigated patients with non-headache onset and indicated that 8% of patients had no headache at the time of admission.[15] From the results of these reports, it is assumed that 8% to 10% of cases exhibit no headache at the time of admission.

These figures seem to show a discrepancy in the common recognition that initial symptoms other than headache are rare.[1,4] Indeed, case reports on atypical onset of SAH have been reported and indicate that initial symptoms other than headache lead to misdiagnosis, because they are rarely recognized.[11-14] The results of this study also show that 14 (3.8%) of 368 cases presented without headache at the onset of SAH, and 4 cases (1.1%) had no headache until the diagnosis of SAH, which was much less rate

than the results of the studies described above. The cooperative studies did not focus on the atypical onset; the initial symptoms leading to admission were not clearly described, and the existence of an interval from onset to admission might also obscure symptoms.[19,20] An investigation by Naganuma M, et al. was performed by sending questionnaires by post to patients 1 to 8 years after their discharge.[15] Ambiguous patient memories concerning the details of SAH onset could yield incorrect results. In this study, the estimation error may be small, because we obtained patient histories from medical records taken under a system by which histories at onset were taken in detail, in order to evaluate the existence of the warning sign and pre-hospitalized rebleeding. The warning sign and rebleeding before hospitalization have been known to affect the course and outcome after neurosurgical management, and the recognition of their existence is clinically important in the management of the SAH patients.[17,18] Of course, in order to clarify the accurate incidence of atypical onset cases, complete prospective studies focusing on it should be performed.

Concerning the initial symptoms, the results of this study show that nausea/vomiting, dizziness/vertigo, and neck pain/back pain were often seen in the atypical onset group.

Nausea/vomiting, which is caused by increased intracranial pressure, is one of the most frequent accompanying symptoms at the onset of SAH.[4,21-23] Dizziness/vertigo can also be seen in some cases at the onset of SAH.[4,22,23] Neck pain/back pain, which is considered to be caused by irritation to the spinal meninges or lumbar theca,[1,14] are also often seen as an accompanying symptom in SAH patients.[4,23] Therefore, most initial symptoms seen in this study are not rare accompanying symptoms of SAH. Symptomatology of the atypical onset of SAH should be established in the future, but it can be stated at present that, to avoid misdiagnosis of atypical onset patients, nausea/vomiting, dizziness/vertigo, and neck pain/back pain with sudden onset should draw attention. Out of these symptoms, nausea/vomiting is considered noticeable, since it was the most common symptom in this study and the recent study has also indicated that the cases of SAH presenting vomiting are often misdiagnosed as digestive organ disease.[24] In addition, elevated blood pressure at the initial medical care might be useful information for diagnosis.

Parenthetically, why did certain patients not exhibit headache at onset? In 7 patients on whom CT scans were performed before rebleeding, SAH grades on CT were Fisher

group 2 or 4 in 4 cases. A thin and localized SAH and / or intracerebral hematoma might not increase intracranial pressure appreciably, or might not irritate pain-sensitive structures at the base of the skull and meninges very much, resulting in lack of sudden headache. However, the remaining 3 cases demonstrated Fisher group 3, and the reason for a lack of headache cannot be explained. Here, the pathogenesis whereby headache is not caused in the atypical onset group should be clarified in the future.

Most important to consider is the extent to which atypical onset influences the primary care of SAH. It has been indicated that misdiagnosis and delayed diagnosis of SAH have often been seen, even in cases that present headache at onset, when the clinical condition is good,[2] the headache is localized or mild,[1,3] or the accompanying symptoms are prominent.[1,3,4] Therefore, in cases of atypical onset, misdiagnosis is assumed to arise more easily and more frequently,[4,14] which was supported by the results of this study. Many reports have indicated that misdiagnosis and delayed diagnosis are significant factors in the morbidity and mortality of SAH by increasing the risk of rebleeding.[2,3,7,8] The results of this study also show a statistically significant higher rate of rebleeding in the atypical onset group, accompanied by a higher rate of

misdiagnosis and delayed diagnosis. A higher rate of rebleeding can lead to poor clinical condition at admission to our institution and a lower rate of operability, resulting in increased poor outcome. Thus, in order to improve overall outcome for SAH patients, it is necessary to pay attention to atypical onset in spite of its lower incidence in SAH cases.

The limitation of this study was that it was performed in a retrospective manner. In order to evaluate accurate incidence and clinical characteristics, a prospective study is essential. After accumulating the results obtained by prospective studies, the clinical importance should be provided to general practitioners, primary care doctors, and emergency doctors in order to decrease misdiagnosis and delayed diagnosis of SAH.

## Conclusions

We investigated the incidence and clinical features of atypical onset of aneurysmal SAH. Atypical onset was seen in 14 (3.8%) of 368 cases with SAH. Such onset is rare but has great impact on the clinical course through rebleeding induced by misdiagnosis or delayed diagnosis, which results in severe clinical conditions on admission and poor

outcomes. A prospective analysis should be performed in future.

## References


1. Edlow JA, Caplan LR. Avoiding pitfalls in the diagnosis of subarachnoid hemorrhage. N Engl J Med 2000;342:29-36.

2. Mayer PL, Awad IA, Todor R, et al. Misdiagnosis of symptomatic cerebral aneurysm. Prevalence and correlation with outcome at four institutions. Stroke 1996;27:1558-1563.

3. Kassell NF, Kongable GL, Torner JC, et al. Delay in referral of patients with ruptured aneurysms to neurosurgical attention. Stroke 1985;16:587-590.

4. Adams HP Jr, Jergenson DD, Kassell NF, et al. Pitfalls in the recognition of subarachnoid hemorrhage. JAMA 1980;244:794-796.

5. Canneti B, Mosqueira AJ, Nombela F, et al. Spontaneous Subarachnoid Hemorrhage with Negative Angiography Managed in a Stroke Unit: Clinical and Prognostic Characteristics. J Stroke Cerebrovasc Dis. 2015 Sep 12. pii: S1052-3057(15)00336-5. doi: 10.1016/j.jstrokecerebrovasdis.2015.06.011. [Epub ahead of print]

6. Beck J, Raabe A, Szelenyi A, et al. Sentinel headache and the risk of rebleeding after aneurysmal subarachnoid hemorrhage. Stroke 2006;37:2733-2737.

7. Kowalski RG, Claassen J, Kreiter KT, et al. Initial misdiagnosis and outcome after subarachnoid hemorrhage. JAMA 2004;291:866-869.

8. Neil-Dwyer G, Lang D. 'Brain attack'—aneurysmal subarachnoid haemorrhage: death due to delayed diagnosis. J R Coll Physicians Lond 1997;31:49-52.

9. van Gijn J, Kerr RS, Rinkel GJ. Subarachnoid haemorrhage. Lancet 2007;369:306-318.

10. Vermeulen MJ, Schull MJ. Missed diagnosis of subarachnoid hemorrhage in the emergency department. Stroke 2007;38:1216-1221.

11. Asplin BR, White RD. Subarachnoid hemorrhage: atypical presentation associated with rapidly changing cardiac arrhythmias. Am J Emerg Med 1994;12:370-373.

12. Brust JC. Subarachnoid hemorrhage: early detection and diagnosis. Hosp Pract 1982;17:73-80.

13. Schattner A. Pain in the neck. Lancet 1996;348:411-412.

14. Weissman MN. Atypical presentation of subarachnoid hemorrhage: case report and review of the literature. WMJ 2002;101:47-50.

15. Naganuma M, Fujioka S, Inatomi Y, et al. Clinical characteristics of subarachnoid hemorrhage with or without headache. J Stroke Cerebrovasc Dis 2008;17:334-339.

16. Mayberg MR, Batjer HH, Dacey R, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage. A statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. Stroke 1994;25:2315-2328.

17. Wilson TJ, Saadeh Y, Stetler WR Jr, et al. Transfer time to a high-volume center for patients with subarachnoid hemorrhage does not affect outcomes. J Stroke Cerebrovasc Dis. 2015;24:416-423.

18. Ohkuma H, Tsurutani H, Suzuki S. Incidence and significance of early aneurysmal rebleeding before neurosurgical or neurological management. Stroke2001;32:1176-1180.

19. Graf CJ, Nibbelink DW. Cooperative study of intracranial aneurysms and subarachnoid hemorrhage. Report on a randomized treatment study. 3. Intracranial surgery. Stroke 1974;5:557-601.

20. Kassell NF, Torner JC, Haley EC Jr, et al. The International Cooperative Study on the Timing of Aneurysm Surgery. Part 1: Overall management results. J Neurosurg 1990;73:18-36.

21. Linn FH, Rinkel GJ, Algra A, et al. Headache characteristics in subarachnoid haemorrhage and benign thunderclap headache. J Neurol Neurosurg Psychiatry 1998;65:791-793.

22. Bassi P, Bandera R, Loiero M, et al. Warning signs in subarachnoid hemorrhage: a cooperative study. Acta Neurol Scand 1991;84:277-281.

23. Fontanarosa PB. Recognition of subarachnoid hemorrhage. Ann Emerg Med 1989;18:1199-1205.

24. Yamada T, Natori Y. Evaluation of misdiagnosed cases of subarachnoid hemorrhage and causal factors for misdiagnosis. J Stroke Cerebrovasc Dis. 2013;22:430-436.

## Figure Legends

**Fig. 1** Flow chart of the clinical course of the atypical onset group

**Fig. 2** Distribution of patients by interval from onset to initial visit to medical care in the headache onset group and the atypical onset group

**Fig. 3** Distribution of patients by interval from onset to diagnosis by CT scan in the headache onset group and the atypical onset group.

* p=0.033, Mann-Whitney U test

**Figure 1** Flow chart of the clinical course of the atypical onset group

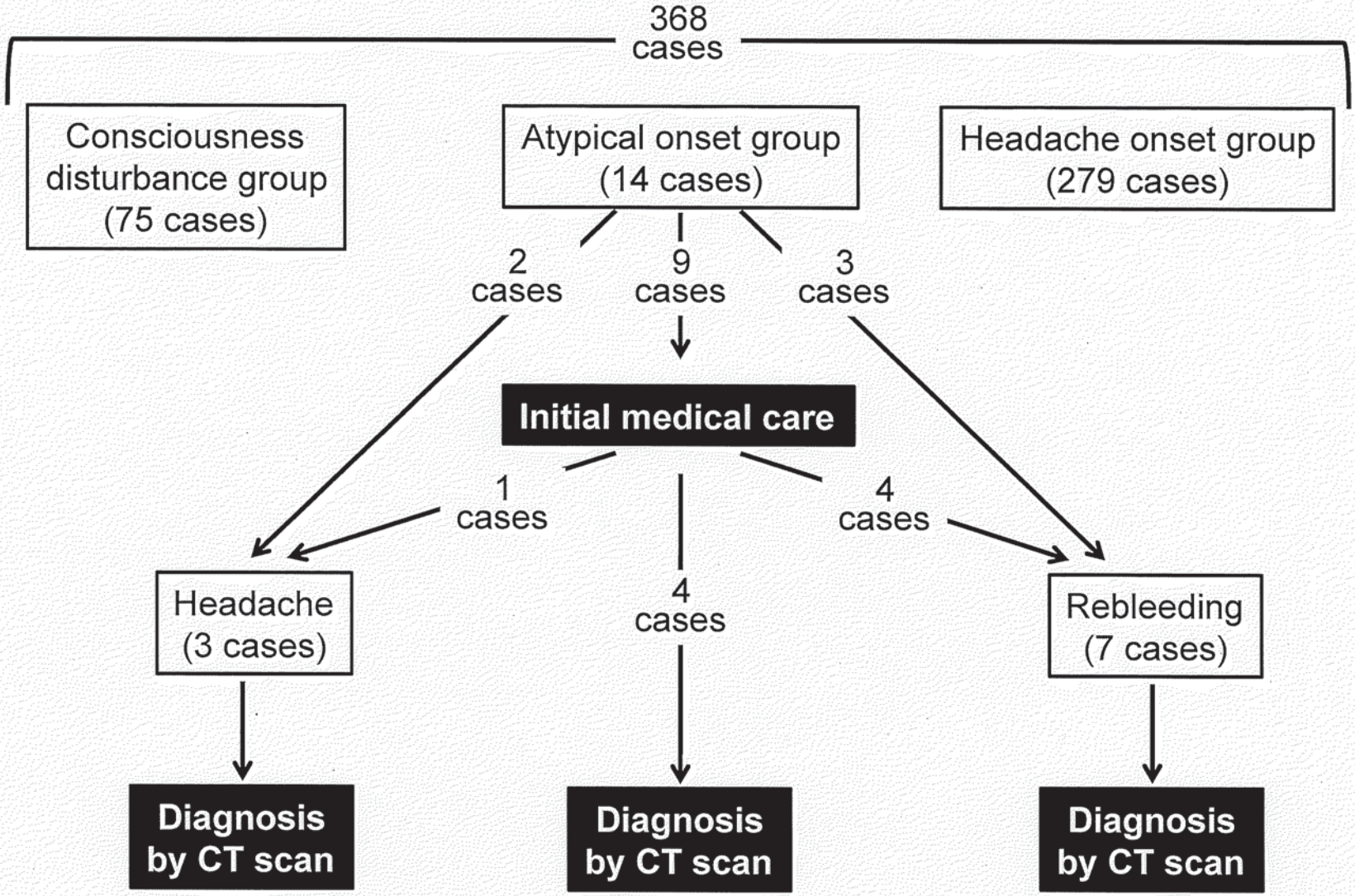

**Figure 2** Distribution of patients by interval from onset to initial visit to medical care in the headache onset group and the atypical onset group

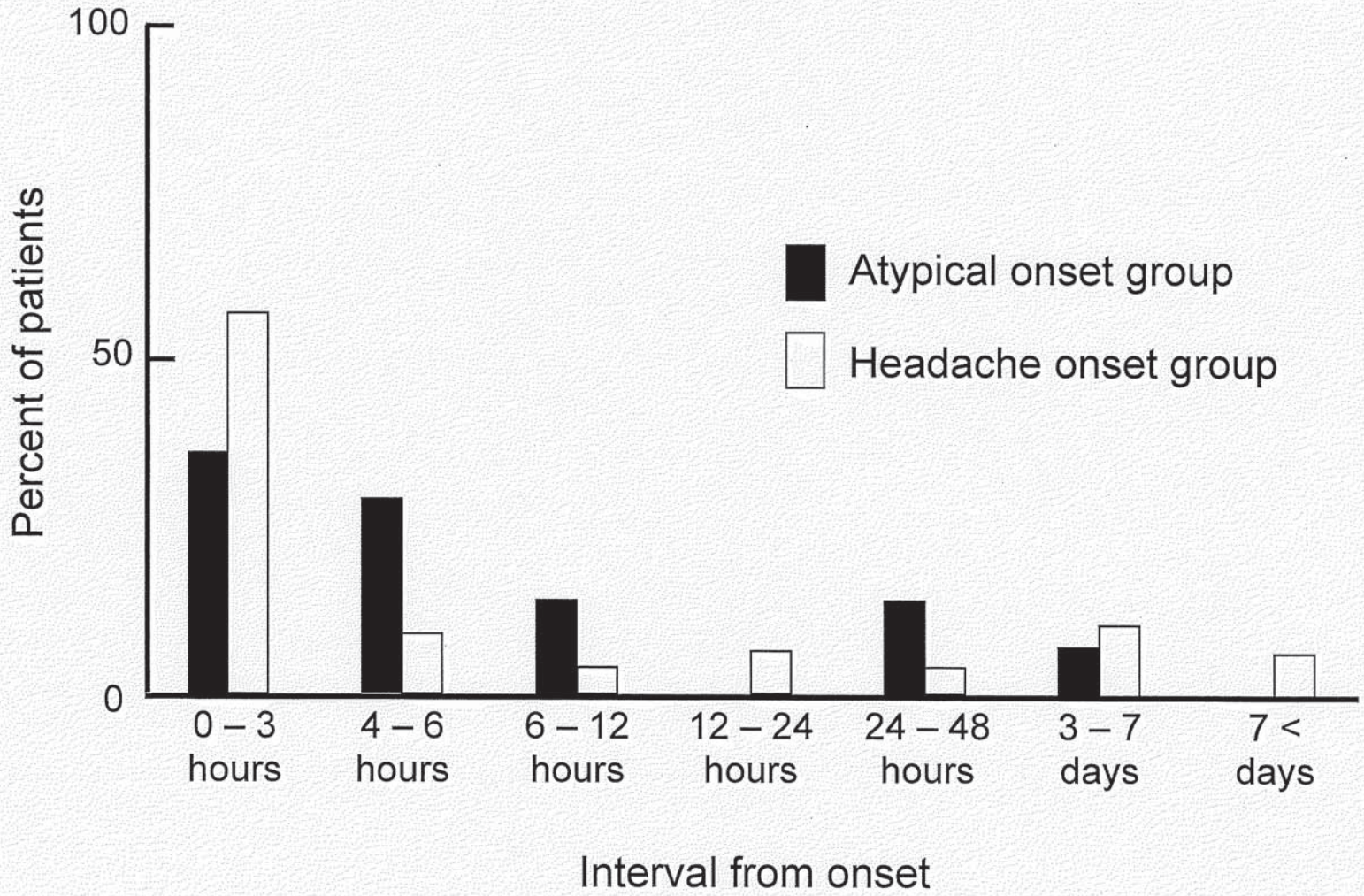

**Figure 3** Distribution of patients by interval from onset to diagnosis by CT scan in the headache onset group and the atypical onset group.

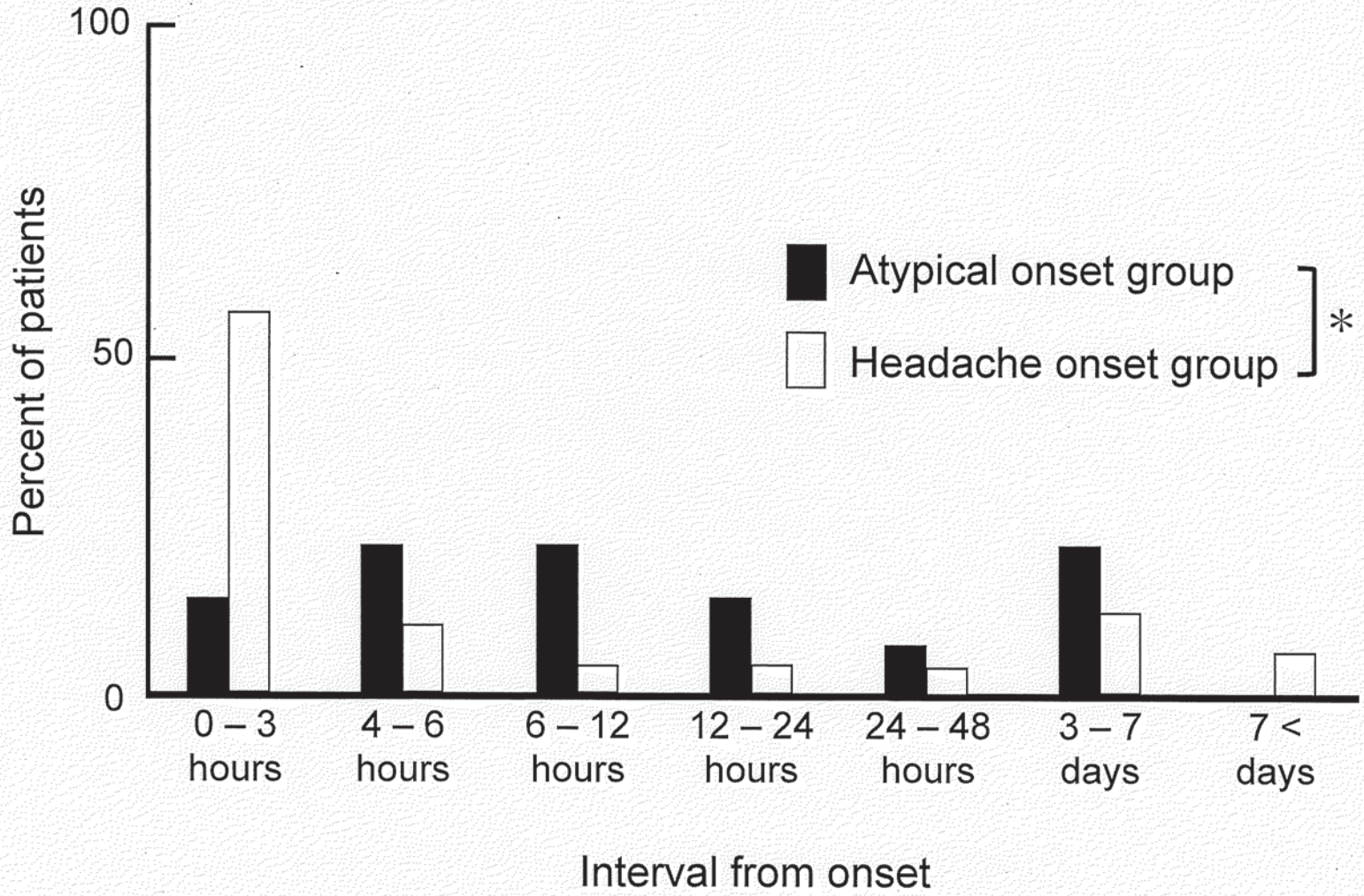

Table 1 Patients characteristics of the headache onset group and the atypical onset group

| | Headache Onset Group | Atypical Onset Group | p Value |
|---|---|---|---|
| No. of cases | 279 | 14 | |
| Age (years), mean ± SD | 60.4 ± 13.0 | 68.2 ± 11.1 | 0.540 |
| Male : Female | 65 : 214 | 3 :11 | 0.872 |
| Initial symptom | | | |
| Headache | 279 (100%) | 0 | <0.001 |
| Nausea / vomiting | 173 (62.0%) | 8 (57.1%) | 0.714 |
| Vertigo / dizziness | 29 (10.4%) | 5 (35.7%) | 0.004 |
| Neck pain / back pain | 45 (16.1%) | 3 (21.4%) | 0.601 |
| The others | 43 (15.4%) | 3 (21.4%) | 0.546 |

SD = standard deviation.

Table 2 Comparison of the parameters before neurosurgical management between the headache onset group and the atypical onset group

| | Headache Onset Group | Atypical Onset Group | p Value |
|---|---|---|---|
| Misdiagnosis | | | |
| at initial medical care in whole cases | 53 / 279 (19.0%) | 5 / 14 (35.7%) | 0.125 |
| at initial medical care excluding prior rebleeding cases | 53 / 262 (20.2%) | 5 / 11 (45.5%) | 0.045 |
| Rebleeding | | | |
| before initial medical care | 17 / 279 (6.1%) | 3 / 14 (21.4%) | 0.065 |
| after misdiagnosis excluding prior rebleeding case | 10 / 53 (18.9%) | 4 / 5 (80.0%) | 0.043 |
| after diagnosis before admission | 6 / 279 (2.2%) | 1 / 14 (7.1%) | 0.233 |
| Total rebleeding before admission | 33 / 279 (11.8%) | 8 / 14 (57.1%) | <0.001 |

Table 3 Comparison of the parameters at the time of admission to neurosurgical institution and after neurosurgical management between the headache onset group and the atypical onset group

| | Headache Onset Group (n=279) | Atypical Onset Group (n=14) | p Value |
|---|---|---|---|
| Hunt & Hess grade | | | 0.009 |
| Grade 1 | 0 (0.0%) | 2 (14.3%) | |
| Grade 2 | 214(76.7%) | 2 (14.3%) | |
| Grade 3 | 38 (13.6%) | 3 (21.4%) | |
| Grade 4 | 21 (7.5%) | 6 (42.9%) | |
| Grade 5 | 6 (2.2%) | 1 (7.1%) | |
| Fisher Group | | | 0.262 |
| Group 1 | 18 (6.5%) | 0 (0.0%) | |
| Group 2 | 51(18.3%) | 3 (21.4%) | |
| Group 3 | 161 (57.7%) | 6 (42.9%) | |
| Group 4 | 49 (17.6%) | 5 (35.7%) | |
| Site of aneurysm | | | 0.150 |
| ACA | 89(31.9%) | 6 (42.9%) | |
| MCA | 67(24.0%) | 5 (35.7%) | |
| ICA | 107 (38.4%) | 3 (21.4%) | |
| VB | 16 (5.7%) | 0 (0.0%) | |
| Operability | 263 (94.3%) | 8 (57.1%) | < 0.001 |
| GOS | | | 0.003 |
| GR | 168 (60.2%) | 3 (21.4%) | |
| MD | 66 (23.7%) | 3 (21.4%) | |
| SD | 20 (7.2%) | 3 (21.4%) | |
| VS | 4 (1.4%) | 2 (14.3%) | |
| D | 21 (7.5%) | 3 (21.4%) | |

ACA = Anterior cerebral artery, ICA = internal carotid artery, MCA = middle cerebral artery, GR = good recovery, MD = moderate disability, SD = severe disability, VS = vegetative state, D = death.