Brief Communication

Reversible cerebral vasoconstriction syndrome: the importance of follow-up imaging within 2 weeks

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Aim: In patients with thunderclap headaches, reversible cerebral vasoconstriction syndrome (RCVS) should be considered as a differential diagnosis. However, RCVS diagnosis in the emergency department (ED) remains challenging. This report describes the clinical features and factors related to RCVS diagnosis and suggests diagnostic strategies for its management.

Methods: We retrospectively reviewed the medical records of eight patients diagnosed with RCVS from January 2010 to March 2019 (aged 18–69 years, 5 women).

Results: The median duration from the ED visit to RCVS diagnosis was 6 days (range, 1–11 days). Of the eight patients, seven were middle-aged, six had apparent triggers, six had subarachnoid hemorrhage (SAH), five had high systolic blood pressure, and none had any specific abnormality observed upon physical examination. At the initial visit, RCVS was diagnosed in only one patient who had a history of RCVS. Of the other patients, SAH was diagnosed in two, and primary headache was diagnosed in four patients with negative computed tomography (CT) findings. Based on follow-up angiography (e.g., magnetic resonance angiography), seven of eight patients with convexal SAH were diagnosed with RCVS (as the cause of SAH).

Conclusion: Reversible cerebral vasoconstriction syndrome with negative CT findings at the ED visit was likely to be misdiagnosed as a primary headache. In patients with thunderclap headache and negative CT findings, physicians should consider RCVS as a differential diagnosis, inform patients of the risk of RCVS, and undertake follow-up imaging within 2 weeks.

Key words: Primary headache, reversible cerebral vasoconstriction syndrome, thunderclap headache

INTRODUCTION

THUNDERCLAP HEADACHE, WHICH refers to a very severe headache of abrupt onset that reaches its maximum intensity within 1 min or less of onset, is implicated in several serious conditions, including aneurysmal subarachnoid hemorrhage (SAH).[1] Recent studies have underscored the importance and prevalence of reversible cerebral vasoconstriction syndrome (RCVS) among patients with thunderclap headache.[2-3]

Reversible cerebral vasoconstriction syndrome is a relatively new disease concept, defined by Calabrese *et al*. in 2007.[4-5] Symptoms of RCVS include thunderclap headache, occasional minor bleeding (as in SAH), and focal neurological symptoms caused by reversible segmental spasms in the cerebral blood vessels.[5] Although RCVS was thought to be a benign condition, recent studies have reported that RCVS can cause premature stroke and recurrent headaches.[6] Despite its clinical importance, there are few emergency department (ED)-based studies and no optimal strategies to manage patients with suspected RCVS.[7]

We describe the clinical features and course of RCVS among eight patients who presented at the ED. We also describe the factors related to RCVS diagnosis and report a strategy to manage patients suspected of having RCVS.

METHODS

WE RETROSPECTIVELY IDENTI fied patients who were diagnosed at Shonan Kamakura General Hospital (Kamakura, Japan) with RCVS between January 2010 and March 2019 using the relevant code from the International Classification of Disease, 10th Revision. We reviewed their medical records for patient characteristics, medical

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Received 17 Jun, 2020; accepted 27 Jul, 2020

history (e.g., triggers of headache), clinical features, diagnostic tests carried out at first ED visit, imaging findings at the time of diagnosis, number of days from onset of headache to diagnosis, and number of days from confirmation of vasospasm. This study was approved by the hospital's Institutional Review Board, and the need for written informed consent was waived.

RESULTS

PATIENT CHARACTERISTICS AND clinical features of the eight RCVS cases are summarized in Table 1. The median age was 55 years (range, 18–69 years), and five patients were women. Seven patients visited the ED for thunderclap headache, and one patient visited for headache with syncope. Based on medical histories, varying causes, including sexual intercourse, beating of drums at a festival, physical or emotional stress, exertion, and urinary tract infection, were thought to be triggers of RCVS. Three patients had comorbidity with migraine or chronic headaches, and one patient had a history of RCVS.

The mean pulse rate, mean systolic blood pressure, and mean diastolic blood pressure were 84 b.p.m. (range, 56–99 b.p.m.), 141 mmHg (range, 95–162 mmHg), and 85 mmHg (range, 57–104 mmHg), respectively. Physical and neurological examinations did not reveal any specific findings (including neck stiffness). Head computed tomography (CT) was carried out at the ED visit in all cases, but abnormalities were only observed in two patients with SAH. Magnetic resonance imaging (MRI) was carried out on three patients, with no specific findings.

Five out of eight patients were initially diagnosed with primary headache. In these patients, there was no history suggestive of RCVS, and four patients were discharged without further instructions. These four patients returned to the ED due to recurrent (or persistent) severe headache and were then diagnosed with SAH (as a comorbid condition of RCVS). Of the three other patients, SAH was diagnosed in two, and RCVS was diagnosed in one. The RCVS patient had a history of RCVS; this patient showed vasospasm on MRI.

Among the seven patients who were not diagnosed with RCVS at the initial visit, follow-up imaging was undertaken within 2 weeks (range, 2–11 days; Table 2). Imaging revealed SAH in all seven cases with a slight pericortical hematoma as a complication of RCVS. These seven patients were diagnosed with RCVS following further assessment of SAH using angiography. None of the patients had an aneurysm. Diagnosis of vasospasm was made using magnetic resonance angiography (MRA), CT angiography, and digital subtraction angiography in five, one, and two patients, respectively. The sites of vasospasm were the middle cerebral artery and diffuse and multiple vessels in three and five patients, respectively. Improvement in vasospasm was later confirmed in seven patients. One patient died of a cause other than intracranial disease.

DISCUSSION

WE FOUND TWO important points for managing patients with suspected RCVS. First, RCVS could be misdiagnosed as primary headache in patients with no complications (e.g., SAH). Second, in patients with thunderclap headache and negative CT findings, RCVS should be considered as a differential diagnosis and the patient should be followed up with imaging (e.g., MRI, MRA) within 2 weeks of the visit. Although RCVS diagnosis is obviously difficult at the ED, management of these patients should be an important basis for emergency care.

Reversible cerebral vasoconstriction syndrome typically occurs in the middle-aged population along with thunderclap headache involving nausea/vomiting.[6] Like other cardio- or cerebrovascular diseases, the presence of triggers could be important. Potential RCVS triggers include use of vasoactive drugs (e.g., triptans and selective serotonin reuptake inhibitors), bathing, and sexual activity.[8,9] In our study, reported characteristics of the eight patients with RCVS are consistent with those described previously and are similar to those of aneurysmal SAH – middle-aged patients (n = 7/8) that visited the ED for thunderclap headache with nausea/vomiting (n = 7/8), apparent triggers (n = 6/8), SAH (hypertension, diabetes, migraine) risk (n = 6/8), high systolic blood pressure (≥140 mmHg) at the ED visit (n = 5/8), and no specific abnormality during physical examination (n = 8/8). There were no specific CT findings in six of the eight patients with RCVS. These results highlight the difficulty in diagnosing RCVS based on present illness, vital signs, and physical findings, although apparent triggers could be somewhat beneficial.

Therefore, in the case of thunderclap headache with negative CT findings, physicians should consider RCVS as a differential diagnosis, inform the patient of the potential risk of RCVS, and record the potential diagnosis in the patient's medical chart for further review.

Additionally, RCVS diagnosis is difficult because of the inconsistency in the duration between the onset of headache and the vasospasm imaging findings. Reversible cerebral vasoconstriction syndrome imaging features are often normal in the early stages of severe headache. Consistent with observations reported in previous studies,[6-8] an average of 8 days was required to confirm vasospasm in this study. Previous studies revealed that vasospasm occurred over time from the peripheral side to the central side of the cerebral artery,[6,10-12] and the appropriate timing of the image

Table 1. Clinical features of eight patients with reversible cerebral vasoconstriction syndrome (RCVS) in the emergency department (ED)

Case number	Age (years), sex	Visit season	Chief complaints	Potential trigger	Comorbidities	Pulse rate, b.p.m.	Blood pressure, mmHg	Physical examinations including neck stiffness	Initial imaging findings	Initial ED diagnosis	Disposition
1	60, F	Autumn	Thunderclap headache	Sexual intercourse	Chronic headache	97	159/104	No abnormality	No specific CT findings	Primary headache (RCVS was not suspected)	Home
2	66, F	Summer	Thunderclap headache, vomiting	Beating drums	None	75	160/95	No abnormality	Finding of cSAH by CT	cSAH	Hospitalization
3	18, M	Autumn	Thunderclap headache, vomiting	Physical and emotional stress (dietary restriction and school exam)	RCVS (2 years ago), migraine	99	95/57	No abnormality	No specific CT findings. Peripheral cerebral vasospasm of the left MCA by MRA	RCVS	Hospitalization
4	51, F	Spring	Thunderclap headache	Unknown	Hypertension, cerebral infarction	92	132/84	No abnormality	No specific CT or MRI findings	Primary headache (RCVS was not suspected)	Home
5	58, F	Summer	Thunderclap headache	Emotional stress (death of her daughter)	Migraine, insomnia	56	148/76	No abnormality	No specific CT findings	Primary headache (RCVS was not suspected)	Home
6	51, F	Winter	Thunderclap headache, nausea	Exertion (ran in a hurry)	Menopausal disorder	72	159/97	No abnormality	No specific CT findings	Primary headache (RCVS was not suspected)	Home
7	65, M	Summer	Headache, syncope	Unknown	Diabetes	85	162/89	No abnormality	Finding of cSAH by CT	cSAH	Hospitalization
8	69, M	Autumn	Thunderclap headache, fever	UTI	Diabetes, chronic kidney disease	92	112/81	No abnormality	No specific CT and MRI findings	UTI, primary headache (RCVS was not suspected)	Hospitalization

cSAH, convexal subarachnoid hemorrhage; CT, computed tomography; F, female; M, male; MCA, middle cerebral artery; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; UTI, urinary tract infection.

Table 2. Clinical course of eight case of reversible cerebral vasoconstriction syndrome (RCVS)

Case number	Time from initial ED visit to RCVS diagnosis (days from onset of headache)	Diagnostic device	Imaging findings and site of spasm	RCVS related complications	Prognosis
1	2 (7)	MRA	Spasm of right MCA (M1)	Frontal lobe cSAH (MRI)	Confirmed improvement of spasm 3 months later by CTA
2	5 (10)	DSA	Spasm of segmental diffuse cerebral artery	Parietal lobe cSAH (CT)	Confirmed improvement of spasm 3 months later by MRA
3	1 (1)	MRA	Spasm of peripheral cerebral artery of left MCA (M2)	None	Confirmed improvement of spasm 1 month later by MRA
4	9 (9)	MRA	Spasm of cerebral artery of right MCA (M2)	Frontal lobe cSAH (MRI)	Confirmed improvement of spasm 6 months later by MRA
5	7 (10)	DSA	Spasm of both sides of PCA and right MCA	Occipital lobe cSAH (MRI)	Confirmed improvement of spasm 3 months later by MRA
6	6 (6)	MRA	Spasm of peripheral cerebral arteries of fornix and posterior circulation	Parietal lobe cSAH (MRI)	Confirmed improvement of spasm 3 months later by MRA
7	11 (13)	MRA	Spasm of both sides of MCA	Left temporal lobe cSAH (CT)	Confirmed improvement of spasm 6 months later by MRA
8	6 (6)	CTA	Spasm of both sides of PCA	Occipital lobe cSAH (CT)	Not checked Death

Two of eight cases (case numbers 4 and 5) received cerebrospinal fluid examination at the repeated emergency department (ED) visits or hospitalization for convexal subarachnoid hemorrhage (cSAH), without any specific findings indicating primary angiitis of the central nervous system. No patients received cerebrospinal fluid examination at the initial ED visit.
CT, computed tomography, CTA, computed tomography angiography; DSA, digital subtraction angiography; M1, M1 segment (horizontal/sphenoidal part) of MCA; M2, M2 segment (insular part) of MCA; MCA, middle cerebral artery; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; PCA, posterior cerebral artery.

evaluation is considered to be 1–2 weeks after the onset of headache.[7] However, by this time, the headache tends to improve,[6] and thereafter, the patients no longer felt they needed treatment.

Although studies have reported that the prognosis of RCVS was generally good, recent studies have indicated the risk concurrent with SAH, as well as other complications in patients with RCVS, such as SAH (22–34%), cerebral hemorrhage (6–12%), and cerebral infarction (4–10%).[5-6,8,13-14] These complications are likely to occur at an early stage.[8] Due to no RCVS-specific findings at the initial patient presentation, these complications could be the key to earlier diagnosis. Conversely, because cerebrovascular complications are reported in 20–30% of RCVS, approximately 70–80% of RCVS patients without complications are likely to be misdiagnosed.

In our study, four patients had slight hematomas that were not detected by CT and required further imaging using MRI. Magnetic resonance imaging could be helpful in distinguishing between SAH and RCVS and other common, non-life-threatening conditions.

Patients with undiagnosed RCVS are at risk of frequent ED visits and of receiving inappropriate therapy. Triggers have been reported in approximately 50%[15] of patients with RCVS, and some of these triggers could help with patient diagnosis. An accurate RCVS diagnosis can improve patient

outcomes. Therefore, accurate diagnosis of RCVS at an early stage is critical.

CONCLUSION

IN EIGHT CASES of RCVS presenting at an initial ED visit, there were no specific findings based on presenting illness, vital signs, physical examination, or CT imaging. As prompt diagnosis of RCVS is difficult at the ED, for patients with thunderclap headache and negative CT findings, physicians should consider RCVS as a differential diagnosis, inform patients of the risk of RCVS, and undertake follow-up imaging within 2 weeks. Early diagnosis of RCVS could result in improved patient outcomes and the reduction of unnecessary ED visits.

DISCLOSURE

Approval of the Research Protocol: This study was approved by the hospital's Institutional Review Board.
Informed Consent: The requirement of written informed consent was waived.
Registry and the Registration no. of the study/trial: N/A.
Animal Studies: N/A.
Conflict of Interest: None.

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