Recurrence of reversible cerebral vasoconstriction syndrome
A long-term follow-up study

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ABSTRACT
Objective: We aimed to investigate whether reversible cerebral vasoconstriction syndrome (RCVS) could recur and to identify the potential predictors of recurrence in a large cohort of patients.

Methods: This study followed a cohort of 210 patients with RCVS in a hospital-based headache center from 2000 to 2012. All patients were regularly followed up by telephone after remission for RCVS and were particularly asked to return to our hospital immediately if they developed new acute, severe (i.e., thunderclap-like) headaches. Sequential neuroimaging studies were used to determine whether the patients had recurrent RCVS.

Results: One hundred sixty-eight patients were successfully followed. The response rate was 80.8%, and the mean follow-up period was 37.5 ± 24.4 (range 6–131) months. Eighteen patients (10.7%) returned to our hospital because of new thunderclap-like headaches, and 9 (5.4% of the total 168, and 50% of 18) were confirmed to have recurrent RCVS that occurred a mean 40.9 ± 27.2 (median 35, range 6–87) months after the initial bout. The incidence rate was 1.71 per 100 person-years (95% confidence interval 1.68–1.75). Having sexual activities as a trigger for thunderclap headaches (hazard ratio 5.68, 95% confidence interval 1.11–29.15, p = 0.038) was an independent predictor of recurrent RCVS. None of the patients with recurrent RCVS developed cerebrovascular complications.

Conclusions: Recurrent RCVS should be considered when patients with RCVS develop new thunderclap-like headaches. Having sexual activities as a trigger for RCVS is a potential predictor of recurrent RCVS.

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GLOSSARY
CI = confidence interval; ICHD-2 = International Classification of Headache Disorders, second edition; ICHD-3-b = International Classification of Headache Disorders, third edition (beta version); LI = Lindegaard index; MRA = magnetic resonance angiography; RCVS = reversible cerebral vasoconstriction syndrome; TCCS = transcranial color-coded sonography; VMCA = flow velocity of middle cerebral artery.

Reversible cerebral vasoconstriction syndrome (RCVS) is a disorder characterized by abrupt, severe headaches (mostly thunderclap headaches) and reversible segmental cerebral vasoconstrictions.1 RCVS is not an uncommon clinical emergency,2–4 but it is still underrecognized.5 A substantial proportion of patients with RCVS experience devastating complications, such as posterior reversible encephalopathy syndrome, ischemic stroke, or intracranial hemorrhages, including cortical subarachnoid, intracerebral, and subdural hemorrhages.2,4,6–8 The pathogenesis of RCVS remains unclear; autonomic dysregulation,9 oxidative stress,10 and genetic predisposition11 may have roles.

RCVS is generally considered a monophasic disease, which is limited to a period of 3 months.12 However, very rare case reports have shown that the recurrence of RCVS could be possible.13,14 In our previous study, 3 (5.4%) of 56 patients reported having previously experienced similar thunderclap headaches 3 months, 6 months, and 1 year before being diagnosed with RCVS.2 In a follow-up study of a French cohort, 2 patients experienced a relapse of
multiple thunderclap headaches 6 months and 3 years after the first bout of RCVS. Although no angiographic studies were available for these prior or follow-up attacks, it is possible that these patients had recurrent RCVS. Considering the potentially hazardous effects of this disease, it is necessary to investigate in what proportion of patients and under what circumstances RCVS recurs after the first bout. To date, no prospective long-term study has examined the recurrence of RCVS. Therefore, the objective of this study was to investigate the recurrence of RCVS and its predictors in a large prospectively recruited cohort.

METHODS Participants and clinical settings. This study prospectively followed patients with RCVS from the headache center of Taipei Veterans General Hospital, a 2,909-bed national medical center in the capital of Taiwan, from December 2000 to December 2012. The diagnosis of RCVS was based on criteria shown in table 1. The criteria were adapted from the proposed diagnostic criteria of “benign (or reversible) angiopathy of the central nervous system” proposed by the International Classification of Headache Disorders, second edition (ICHD-2; code 6.7.3), with the exception of the duration criterion D (i.e., headache [and neurologic deficits, if present] resolves spontaneously within 2 months), and the RCVS diagnostic elements proposed by Calabrese et al. The criteria were also in concordance with the newly proposed criteria for “headaches attributed to RCVS” in the ICHD, third edition (beta version) (ICHD-3-b; code 6.7.3) (table 1). In fact, all of our patients (n = 210, 100%) fulfilled the new ICHD-3-b criteria.

Diagnostic evaluations and treatment for the first bout of RCVS. The diagnostic procedures and interventions have been reported elsewhere and are briefly summarized in table 2. All of the investigations were performed within the first 2 days after the patient was seen. Patients were placed on oral (30–60 mg every 4 hours) or IV (0.5–2 mg/h) nimodipine therapy with close blood pressure monitoring immediately after confirmation of cerebral vasospasms and exclusion of other possible causes of thunderclap headaches, especially aneurysmal subarachnoid hemorrhage. All patients were instructed to avoid triggers for thunderclap headaches before the resolution of vasospasms.

All patients were regularly followed up at the headache clinic with gradual tapering of nimodipine if they were on it according to clinical symptoms. Sequential magnetic resonance angiography (MRA) and transcranial color-coded sonography (TCCS) were performed to ensure the reversibility of vasospasms regarding both diagnosis and treatment. Mean flow velocity of middle cerebral artery (V_{MCA}) and the Lindegaard index (LI), and the MRA vasospasm scores in the major intracranial arterial segments were recorded. All patients were regularly seen at the headache clinic until there were no more thunderclap headache attacks and there was complete or at least marked resolution of the vasospasms. This first bout of RCVS disease course was defined as initial RCVS.

Follow-ups. After remission of RCVS, the patients entered our follow-up program (figure 1). All patients were instructed to self-monitor their headaches and neurologic symptoms, and received telephone follow-ups to assess their headache statuses. Some patients were followed up at our headache clinic on a regular basis for small lingering headaches or preexisting migraines that required medical attention. All patients were particularly instructed to return to our hospital immediately if they developed new headaches. If the new headaches were thunderclap headache–like, that is, acute severe attacks that reached maximum intensity immediately, then the patients underwent the same diagnostic evaluations as they did during their first bout of RCVS. The same diagnostic criteria as the first bout of RCVS (table 1) were also applied for the diagnosis of recurrent bouts of RCVS. Patients who were lost to follow-up 6 months after the onset of their first bout of RCVS were defined as nonrespondents, and patients who were able to respond to at least one telephone or headache clinic follow-up after 6 months were defined as respondents.

Standard protocol approvals, registrations, and patient consents. The study protocol was approved by the institutional review board of Taipei Veterans General Hospital. All participants provided written informed consent before entering the study. All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki. The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit the research for publication.

Statistics. All analyses were performed with the IBM SPSS Statistics software package, version 18.0 (SPSS, Inc., Chicago, IL).
Descriptive statistics are presented as the mean ± SD, median (range), or as the number (percentage). Student t, Fisher exact, or χ² tests were used for comparisons between groups when appropriate. Paired t-test or Wilcoxon signed-rank test was used to compare paired data. Cox regression model was used to determine variables independently associated with recurrence. All calculated p values were 2-tailed. Statistical significance was defined as a p < 0.05.

RESULTS Patients and their characteristics. The RCVS cohort. We recruited 210 patients with RCVS during the 12-year study period (table e-1 on the Neurology® Web site at Neurology.org). By the end of the study, 2 patients died of malignancies and 40 patients were lost to follow-up (nonrespondents). Hence, 168 patients (80.8%, respondents) were eligible for the final
The associated symptoms in these patients recurred with probable RCVS were female, and their headaches were most frequently explosive at onset with severe intensity (10 to 15 minutes and fulfilled the diagnostic criteria of migraine. The headaches of the other patient were unclassified because the patterns of the headaches did not differ from that in patients without recurrence (n = 159) (maximum VMCA: 104.8 ± 27.9 cm/s vs 99.8 ± 40.0 cm/s, p = 0.726; maximum LI: 2.14 ± 0.41 vs 2.24 ± 0.89 cm/s, p = 0.775). All patients had multisegmental arterial stenosis according to the MRA during both bouts (figure 2). The TCCS was performed on the same day as the MRA, and the maximum mean vasoconstriction score, V_{VMCA}, and LI are shown in table e-2. There was no difference in the combined vasoconstriction score between the first and recurrent bouts (p = 0.213, Wilcoxon signed-rank test).

Risk factors for recurrent RCVS. Clinical variables including demographics, medical illness, and headache triggers during the first bout of RCVS were assessed to see whether they could predict the recurrence of RCVS using a Cox regression model (table e-3). Univariate analysis showed that having sexual activities as a trigger for thunderclap headaches in the first bout of RCVS was an independent predictor for recurrent RCVS. The multivariable analysis showed that sexual activities as a trigger had a hazard ratio of 3.95 (95% CI 1.01–15.38, p = 0.048) as a trigger for thunderclap headaches in the first bout of RCVS was an independent predictor for recurrent RCVS. The multivariable analysis showed that sexual activities as a trigger had a hazard ratio of 5.68 (95% CI 1.11–29.15, p = 0.038).

Characteristics of patients who recurred with probable RCVS. Six patients (3.5%) with new thunderclap-like headaches were diagnosed with probable RCVS (figure 1), which occurred a mean 48.2 ± 30.1 (median 48, range 15–106) months after the previous bout with RCVS. For the remaining 3 patients who experienced new “thunderclap-like headache,” 2 were diagnosed as acute migraine because their acute severe headaches actually reached peak intensity in around 10 to 15 minutes and fulfilled the diagnostic criteria of migraine. The headaches of the other patient were unclassified because the patterns of the headaches were inconsistent and poorly defined. The MRAs of all these 3 patients were negative. All the patients who recurred with probable RCVS were female, and their first bout of RCVS occurred at a mean age of 47.7 ± 11.2 years. None of these patients had identifiable...
causes for their first bout of RCVS or the subsequent bout of probable RCVS. These patients were diagnosed with probable RCVS because their MRA (2 examinations in 4 patients and 1 examination in 2 patients) and TCCS (2 examinations in 3 patients and 1 examination in 3 patients) results showed no significant vasoconstriction.

**DISCUSSION** In this prospective long-term follow-up study of a large cohort of patients with RCVS, we found that 5% of the patients had recurrent RCVS with an incidence rate of 1.71 per 100 person-years (95% CI 1.68–1.75). These results conflict with the common notion that RCVS is a monophasic disease. The chance of recurrent RCVS was high (50%) in patients who developed new thunderclap-like headaches. Having sexual activity as a trigger for thunderclap headaches was the only risk factor found for recurrent RCVS. The recurrent bouts of RCVS were not associated with higher rates of complications. None of our patients developed aneurysmal subarachnoid hemorrhage.

We found that recurrence of RCVS could happen as early as 6 months and as late as 7 years after the first bout. In the 2 previously reported cases of recurrent RCVS, one had recurrent postpartum angiopathy that occurred 32 months after the first bout, and the other experienced a relapse after tapering therapy during a 43-month follow-up period (the exact timing of the relapse was not reported). Hence, although the risk of RCVS recurrence was not high, it could not only be imminent after tapering treatment, but also be long-lasting. The occurrence of new thunderclap-like headaches should be considered as the most alarming symptom of RCVS recurrence. Once new thunderclap-like headaches occur, thorough investigations must be performed again. The characteristics of patients with recurrent RCVS were not distinctly different from the entire RCVS cohort; however, if the patients had sexual activity as a trigger during their first bout, a higher risk of recurrence should be warned. In the era before knowing that RCVS is an important cause for sexual headaches (now coded as 4.3 primary headache associated with sexual activity in the ICHD-3-b), patients with recurrent sexual headaches were usually treated as having a new episode of primary headache associated with sexual activity. If the patients have received comprehensive neurovascular investigations that disclose reversible vasoconstrictions, these patients should be diagnosed as having recurrent RCVS instead of recurrent primary headache associated with sexual activities. In addition, although not identified in our series, 2 historical cases with recurrent RCVS had hemorrhagic
Comment: Reversible cerebral vasoconstriction syndrome can hit twice

Rare cases with recurrent reversible cerebral vasoconstriction syndrome (RCVS) have been published. The authors analyzed the recurrence risk of RCVS in a large Taiwanese cohort; 210 patients with a definite RCVS were followed up during a mean period of about 3 ± 2 years, with slightly less than 20% of cases lost to follow-up, leaving 168 patients for the final analysis. The main result is that RCVS can hit twice. Recurrence occurred in a minority of cases (9 of the 168 patients, 5%) with a delay from the first to the second bout ranging from 6 months to 7 years. All initial RCVS were idiopathic. Recurrent RCVS was idiopathic in 8 cases and triggered by a vasoactive drug in one. Both initial and recurrent RCVS were benign, namely, purely cephalalgic without any focal deficit, stroke, or brain edema. Having sexually triggered thunderclap headaches during the initial RCVS was an independent predictor of recurrence.

The observed 5% recurrence rate of RCVS within the first few years applies only to the study population, which included a vast majority of cases with idiopathic and purely cephalalgic RCVS. Follow-up studies of the US2 and the French3 cohorts are awaited to determine the recurrence risk in the more severe cases, namely, those in whom RCVS was associated with headache and cerebral lesions including brain edema, convexity hemorrhage, or parenchymal stroke, and those in whom RCVS occurred postpartum or after drug exposure.

These results should be transmitted to our patients who are often very anxious after recovery from a first RCVS. The majority of patients do well, without recurrence during the first years. However, new thunderclap headaches after a first RCVS should raise suspicion of a recurrence, and prompt new parenchymal and arterial cerebral imaging.


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AUTHOR CONTRIBUTIONS

Dr. S.-P. Chen: study concept and design, acquisition of data, analysis and interpretation, manuscript writing. Dr. J.-L. Fuh: study concept and design, study supervision, critical revision of the manuscript for important intellectual content. Dr. J.-F. Lirng: acquisition of data, analysis and interpretation. Dr. Y.-F. Wang: acquisition of data, analysis and interpretation. Dr. S.-J. Wang: study concept and design, study supervision, critical revision of the manuscript for important intellectual content.

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