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ORIGINAL ARTICLE

Type of headache at onset and risk for complications in reversible cerebral vasoconstriction syndrome

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Abstract

Background: In a recent Italian study, 30% of patients with reversible cerebral vasoconstriction syndrome (RCVS) presented without thunderclap headache (TCH), and tended to present more severe forms of RCVS than patients with TCH. We aimed to analyze the risk for complications of RCVS in patients with and without TCH at onset.

Methods: In a pooled cohort of 345 French patients with RCVS, we compared patients with and without TCH at onset regarding rates of neurological complications, and the functional outcome at 3 months.

Results: As compared to the 281 patients with TCH at onset, the 64 patients without TCH had a higher risk for any neurological complication (61% vs. 24%, OR 4.9, 95% CI 2.8–8.7, $p < 0.001$). The association was strongest for cervical artery dissections (28% vs. 5%, OR 8.1, 95% CI 3.7–17.6, $p < 0.001$), followed by posterior reversible encephalopathy syndrome (17% vs. 3%, OR 7.1, 95% CI 2.7–18.4, $p < 0.001$), seizures (9% vs. 2.5%, OR 4.1, 95% CI 1.3–12.5, $p = 0.019$), and subarachnoid hemorrhage (41% vs. 16%, OR 3.5, 95% CI 1.9–6.3, $p < 0.001$). In multivariable analysis, the risk for any neurological complication remained significantly elevated in the absence of TCH (OR 3.5, 95% CI 1.8–6.8, $p < 0.001$). The functional outcome was equal in both groups, with a modified Rankin scale score of 0–1 in ≥90% of patients.

Conclusions: Absence of TCH at onset might predict a higher risk of complications in RCVS. Our results warrant further multicentric studies to prove this finding.

KEYWORDS
calcitonin gene-related peptide, cerebrovascular diseases, reversible cerebral vasoconstriction syndrome, stroke, thunderclap headache

INTRODUCTION

Reversible cerebral vasoconstriction syndrome (RCVS) consists of headache and multisegmental cerebral vasoconstriction which is reversible within 3 months. Neurological complications occur in 10%–79% of patients [1–3]. The functional outcome is favorable, with complete recovery in the large majority of patients [4,5].

There is little evidence on the risk factors for complications. A previous analysis of our cohort found an association of female sex and migraine with hemorrhagic forms of RCVS [6] and several studies documented more complications in patients with secondary compared to idiopathic RCVS [3,7]. Singhal et al. identified use of serotonergic antidepressants prior to RCVS and glucocorticoid treatment after onset of RCVS as risk factors for clinical and radiologic worsening [8].

Typically, RCVS presents with thunderclap headache (TCH), but up to 32% of patients relate other types of headaches [3], or no headache at all [9]. In a recent Italian study, patients who presented without TCH had a tendency to present more often with ischemic strokes and seizures [3].

We aimed to analyze the risk for neurological complications and for a poor clinical outcome depending on the type of headache at onset.

METHODS

Study design and selection criteria

This was a pooled analysis of one prospective and two retrospective RCVS cohorts which were recruited at the French University Hospitals of Paris Lariboisière and Montpellier.

At Lariboisière Hospital, all consecutive patients with proven RCVS were prospectively included from 2004 to 2011 (cohort A, $n = 173$). Seventy percent of patients were recruited from the emergency headache clinic (EHC), and 30% from the neurological ward including a stroke unit. Inclusion criteria, patient characteristics, treatment, and assessment of reversibility of vasoconstriction have been described previously [10,11].

After the end of the prospective study, patients were retrospectively included from 2012 to 2015, following the same inclusion criteria (cohort B, $n = 132$). Eighty percent of patients were recruited from the EHC, and 20% from the neurological ward. Reversibility of cerebral vasoconstriction was proven in all patients either by angiography or by transcranial Doppler.

At the University Hospital of Montpellier, patients were retrospectively identified by searching the electronic database for the International Classification of Diseases codes I67.84 and I67.9 from 2016 to 2019. For all cases identified (cohort C, $n = 40$), we analyzed medical records to ensure that they met the abovementioned inclusion criteria [10,11]. All identified patients had been admitted to the neurological ward. Reversibility was proven by angiography in 93% of patients. The remaining three patients had purely cephalalgic RCVS with recurrent TCHs, absence of parenchymal lesions, and a self-limited clinical course in the absence of immunosuppressant treatment.

Ethics approvals were obtained from the respective local institutional review boards. The database used in the study was approved by the Commission Nationale Informatique et Liberté. The study was performed in accordance with the Declaration of Helsinki.

Definitions of clinical characteristics

We classified patients according to the type of headache at onset. TCH was defined as a headache reaching a maximum intensity above 7/10 on an 11-point scale from 0 to 10, in <1 min. For other types of headache, intensity was defined as excruciating for an intensity of 9–10/10, as severe for an intensity of 7–8/10, as moderate for an intensity of 5–6/10, as mild for an intensity of 3–4/10, and as minimal for an intensity of 1–2/10, respectively. Patients who woke up with a headache of maximum intensity were not classified as having TCH since the mode of onset was unknown. Patients who did not report TCH at onset but during the course of illness were classified as patients without TCH at onset.

We assessed the delay between onset, namely the first episode of headache or neurological deficit, and the first neurological examination. RCVS was qualified as secondary in the presence of a potential precipitating factor and as idiopathic when none could be identified.

We analyzed the risk for any neurological complication including a neurological deficit with persistence >24 h, seizure, brain lesions (ischemic stroke [IS], intracerebral hemorrhage [ICH], subarachnoid hemorrhage [SAH], subdural hematoma [SDH], posterior reversible encephalopathy syndrome [PRES], and cervical artery dissections [CAD]).

Functional outcome was assessed by the modified Rankin Scale (mRS) at clinical follow up at 3 months for the prospective cohort, and retrieved from patient files for the retrospective cohorts.

Statistical analysis

Continuous variables were presented as mean (standard deviation [SD]) if normally distributed and as medians (interquartile range [IQR]) if not normally distributed. Categorical variables were presented as numbers (%).

Characteristics were compared between the three cohorts by Pearson's chi-squared test for categorical variables, and by ANOVA and Kruskal–Wallis test for normally distributed and non-normally distributed continuous variables, respectively.

For comparison of two groups, categorical variables were compared by the Fisher exact test or Pearson's chi-squared test depending on the sample size. For continuous variables, Student's *t*-test was applied for comparison of sufficiently normally distributed data and the Mann–Whitney U-test for non-normally distributed data. The mRS was dichotomized as 0–1 versus 2–6. For univariable analysis, we indicate odds ratios (OR) and their 95% confidence intervals (CIs) from Pearson's chi-squared test.

Characteristics between patients with and without complications were compared in order to identify possible confounders. To determine independent associations of the absence of TCH and neurological complications, we performed a stepwise forward logistic regression for estimation of multivariable OR and their 95% CI, with adjustment for variables associated with the absence of TCH and/or the occurrence of neurological complications. Patients with missing values for one of the covariables were excluded from multivariate analysis. In a second step, in order to confirm our findings, we performed a sensitivity analysis on the prospective cohort only. Results were considered to be significant at a two-sided alpha-level of 0.05.

All statistical analyses were conducted using SPSS 25 (SPSS Inc., Chicago, IL, USA).

RESULTS

Clinical cohort characteristics

Table 1 displays patient characteristics of the overall study cohort at onset and follow-up, and according to presence or absence of TCH. The cohort consisted of 66% female patients; mean age was 42 (SD 13) years. In 36% of patients RCVS was considered idiopathic. Neurological examination was performed with a median delay of 5 [IQR 3–9] days after onset of symptoms. Any neurological complication occurred in 31% of patients, with SAH, CAD, and ICH being the most frequent types of complications.

Comparison between the three combined cohorts of RCVS patients is presented in Table S1. In cohorts A and B, the percentage of patients recruited from the neurological ward was significantly lower than in cohort C. History of migraine, arterial hypertension, and anxiety or depression was significantly more often reported by patients from cohort A. Secondary causes for RCVS, especially emotional stress, as well as blood pressure surge and neurological complications, were more frequent in cohorts A and C.

Comparison of patients with and without TCH at onset

Type of headache at onset is detailed in Figure 1. Sixty-four patients (19%) presented without TCH at onset. Of those, 42 patients reported headache with defined onset other than TCH, 13 woke up with headache, three related isolated neck pain, and six patients presented with seizure or a focal deficit. All patients with isolated neck pain had CAD. Twenty-seven patients did not report any TCH during the course of disease. Patients who presented without TCH at onset were significantly more often female ($p < 0.001$), had more often a history of migraine ($p = 0.005$), and had more often secondary RCVS ($p = 0.034$), including postpartum RCVS ($p < 0.001$, Table 1). There was no difference concerning the delay between onset of symptoms and first neurological exam, and the percentage of patients having received treatment by a calcium antagonist was equal.

Neurological complications occurred significantly more often in patients without TCH at onset (61% vs. 24%, $p < 0.001$), who were significantly more often affected by seizures (9% vs. 2.5%, $p = 0.019$), SAH (41% vs. 16%, $p<0.001$), PRES (17% vs. 3%, $p < 0.001$), and CAD (28% vs. 5%, $p < 0.001$), while the rate of a persistent neurological deficit, IS, ICH, and SDH was not different.

Type of headache and risk for neurological complications

In univariable analysis, the risk for any neurological complication was higher in patients without TCH at onset (OR 4.9, 95% CI 2.8–8.7, $p < 0.001$). The association was strongest for CAD (OR 8.1, 95% CI 3.7–17.6, $p < 0.001$), followed by PRES (OR 7.1, 95% CI 2.7–18.4, $p < 0.001$), seizures (OR 4.1, 95% CI 1.3–12.5, $p = 0.019$), and SAH (OR 3.5, 95% CI 1.9–6.3, $p < 0.001$). Other risk factors for complications were female sex, older age, migraine, history of anxiety or depression, postpartum status, and blood pressure surge during RCVS. Prior use of serotonergic antidepressants was not a risk factor.

Results of multivariable analysis are displayed in Table 2a (patients without missing values for any of the covariables, $n = 335$). After adjustment for the abovementioned potential confounders, the absence of TCH at onset was still an independent risk factor for any neurological complication (OR 3.5, 95% CI 1.8–6.8, $p < 0.001$). Female sex, older age, history of anxiety or depression, postpartum status, and blood pressure surge during RCVS were also independently associated with the occurrence of neurological complications. With regard to the subtypes of complications, the absence of TCH at onset was independently associated with CAD (OR 5.5, 95% CI 2.2–12.2, $p < 0.001$), PRES (OR 4.5, 95% CI 1.5–13.5, $p = 0.037$), and SAH (OR 3.0, 95% CI 1.5–5.9, $p = 0.002$).

Sensitivity analysis

Multivariable analysis on the prospective cohort only confirmed an independent association of the absence of TCH and neurological complications (OR 2.6, 95% CI 1.1–6.2, $p = 0.037$, Table 2b). Other independent risk factors for complications were female sex and postpartum status.

Functional outcome

The functional outcome was excellent in the entire cohort, with a mRS score of >1 in less than 5% of patients at 3 months' follow-up (Table 1).

DISCUSSION

We identified a significant association of the absence of TCH with the risk for neurological complications in patients with RCVS. The association remained significant after adjustment for confounders.

Our results are in line with the findings from the Italian cohort concerning a higher risk for seizures in patients without TCH at onset [3]. In contrast, we did not observe an elevated risk for IS, but for CAD, PRES, and SAH.

The clinical outcome at 3 months' follow-up was very good independent of the type of headache at onset.

To date, there is little evidence for a possible association between the type of headache at onset and the risk for neurological complications. A literature review on RCVS patients without TCH found complications including IS and ICH, SDH, SAH and PRES in 54/57 of patients, considerably exceeding the prevalence of complications in patients with TCH seen in other studies [9].

TABLE 1 Clinical characteristics and outcome, comparison of reversible cerebral vasoconstriction syndrome patients with and without thunderclap headache at onset

Variable	All ($n = 345$)	TCH at onset ($n = 281$)	No TCH at onset ($n = 64$)	p value
Female sex	228 (66)	173 (62)	55 (86)	<0.001
Age, years	42 (13)	42 (13)	42 (12)	0.682
Comorbidities				
Arterial hypertension	37 (11)	28 (10)	9 (14)	0.339
Migraine	92 (27)	66 (23.5)	26 (41)	0.005
Current smoking	110 (32)	95 (34)	15 (23)	0.108
Anxiety or depression	73 (21)	60 (21)	13 (20)	0.854
Precipitating factors				
None	126 (36)	110 (39)	16 (25)	0.034
Physical stress	97 (28)	65 (23)	32 (50)	<0.001
Postpartum	29 (8)	14 (5)	15 (23)	<0.001
Other types of physical stress	68 (20)	51 (18)	17 (27)	0.127
Emotional stress	74 (21)	63 (22)	11 (17)	0.357
Vasoactive substance	148 (43)	123 (44)	25 (39)	0.492
Clinical manifestations				
Delay from onset to neurological exam, days	5 (3–9)	6 (3–9)	4 (1–8)	0.016
BP surge (missing = 10)	77 (23)	10 (4)	20 (31)	0.065
Any neurological complication[a]	107 (31)	68 (24)	39 (61)	<0.001
Persistent focal neurological deficit >24 h	26 (7.5)	18 (6)	8 (12.5)	0.085
Seizure	13 (4)	7 (2.5)	6 (9)	0.019
Radiological manifestations				
Any brain lesion[b] or cervical artery dissection	105 (30)	66 (24)	39 (61)	<0.001
Ischemic stroke	17 (5)	12 (4)	5 (8)	0.332
Intracerebral hemorrhage	21 (6)	17 (6)	4 (6)	1.000
Subdural hematoma	4 (1)	3 (1)	1 (2)	0.562
Subarachnoid hemorrhage	72 (21)	46 (16)	26 (41)	<0.001
PRES	19 (5)	8 (3)	11 (17)	<0.001
Cervical artery dissection	31 (9)	13 (5)	18 (28)	<0.001
Treatment				
Treatment by calcium antagonist (missing=7)	322 (93)	263 (94)	59 (92)	0.765
Functional outcome				
mRS at 3 months' follow-up				1.000
0–1	333 (96.5)	271 (96)	62 (97)	
≥1	12 (3.5)	10 (4)	2 (3)	

Note: Values are given as mean (SD) or median (IQR) for continuous data and as n (%) for categorical data. Values of p from Fisher's exact test or Pearson chi-squared test for categorical variables, Mann–Whitney U-test for non-normally distributed continuous variables, and independent t-test for normally distributed continuous variables.

Abbreviations: BP surge, blood pressure surge >160/90 mmHg; missing, missing values; mRS, modified Rankin Scale score; PRES, posterior reversible encephalopathy syndrome; TCH, thunderclap headache.

[a]Including any focal neurological deficit >24 h, seizures, ischemic stroke, intracerebral hemorrhage, subdural hematoma, subarachnoid hemorrhage, PRES, and cervical artery dissection.

[b]Including ischemic stroke and intracerebral hemorrhage, subdural hematoma, subarachnoid hemorrhage, and PRES.

One French study included young ischemic stroke patients of which 21 patients had IS due to RCVS. Among these patients, none had TCH, and 26% had no headache at all [12]. It was supposed that a RCVS variant might be responsible for the particular clinico-radiological presentation.

As regards possible explanations, first, one could assume that patients without TCH present later, causing a delay in diagnosis and treatment, thus leading to more neurological complications. However, in our cohort, the delay between onset of symptoms and the first neurological exam was similar between patients with and

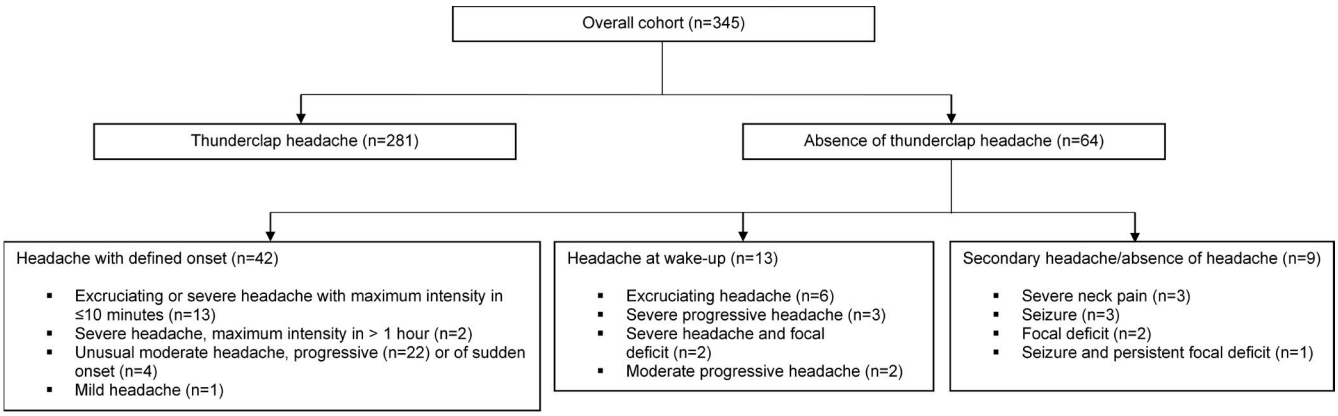

FIGURE 1 Clinical spectrum of headache at reversible cerebral vasoconstriction syndrome onset. Diagram detailing the clinical presentation at onset. Thunderclap headache was defined as a headache reaching a maximum intensity above 7/10 on an 11-point scale from 0 to 10, in <1 min. Headache intensity was defined as excruciating for an intensity of 9–10/10, as severe for an intensity of 7–8/10, as moderate for an intensity of 5–6/10, as mild for an intensity of 3–4/10, and as minimal for an intensity of 1–2/10, respectively

TABLE 2 Multivariable analysis on the association of clinical characteristics and occurrence of any neurological complication (n = 335)

Outcome	Variable	OR (95% CI)	p value
(A) Pooled cohorts A–C (n = 335[a])			
Any neurological complication[b]	Postpartum	8.5 (2.9–24.5)	<0.001
	Absence of TCH at onset	3.5 (1.8–6.8)	<0.001
	Female sex	2.6 (1.2–5.4)	0.013
	Anxiety or depression	1.9 (1.0–3.6)	0.041
	BP surge	1.9 (1.0–3.4)	0.043
	Age (per 1 year increase)	1.04 (1.01–1.06)	0.006
(B) Prospective cohort A (n = 173)			
Any neurological complication[b]	Postpartum	6.2 (1.3–29.8)	0.022
	Female sex	4.8 (1.9–11.7)	0.001
	Absence of TCH at onset	2.6 (1.1–6.2)	0.037

Note: OR (95% CI) and p value from stepwise forward logistic regression including the variables thunderclap headache at onset, sex, migraine, postpartum, anxiety or depression, BP surge, and age.

Abbreviations: BP surge, blood pressure surge >160/90 mmHg; CI, confidence interval; OR, odds ratio; TCH, thunderclap headache.

[a]Patients with missing values for one of the covariates were excluded from multivariate analysis (n = 10).

[b]Including any focal neurological deficit >24 h, seizures, ischemic stroke, intracerebral hemorrhage, subdural hematoma, subarachnoid hemorrhage, posterior reversible encephalopathy syndrome, and cervical artery dissection.

without TCH. Of note, we analyzed the delay from onset until the first neurological exam. Patients' routes were very heterogenous, with patients presenting directly to the headache emergency clinic, and others having consulted several non-neurologists before.

Second, it is possible that RCVS is underdiagnosed in patients who have neither TCH nor complications, hereby leading to a selection bias. These patients might not consult, or might not receive adequate brain imaging. In patients without TCH but with complications, RCVS might be diagnosed mainly due to the complications.

Third, both the type of headache at onset and the risk of complications could be influenced by the mechanisms regulating cerebral arterial tone, and at least in part by the calcitonin gene-related peptide (CGRP)-dependent trigeminovascular reflex. On the one hand, CGRP is a potential mediator of headache, and on the other hand it induces vasodilatation [13]. In migraine, CGRP is known as a key mediator and biomarker [14], and therapeutic approaches targeting CGRP have consistently shown efficacy for the treatment and prevention of migraine attacks [15]. In RCVS, sympathetic overactivity leading to vasoconstriction could result in an activation of the trigeminovascular reflex, and thereby in CGRP secretion. Different levels of CGRP secretion, and different levels of sensitivity to CGRP regarding its pain-inducing capacities and its vasodilation potency, may play a role in the features of headache and in an individual's vulnerability to complications. To date, studies measuring CGRP levels in patients with RCVS do not exist. Yet, an exploration of a possible link between CGRP levels, type of headache, and risk for complications might be pertinent, given the potential therapeutic consequences.

In our cohort, RCVS patients more often had complications than in the Japanese [16], Korean [7], and Taiwanese [2] cohorts, and less often than in an Italian [3] and two American cohorts [17,18].

Concerning the subtypes of complications, the proportion of CAD was higher in our cohort, whereas not all of the abovementioned studies indicated whether carotid imaging had been performed. Of note, from the different subtypes of complications, the absence of TCH was most strongly associated with CAD. To date, it remains unknown whether RCVS induces CAD or vice versa. Twenty patients presenting with RCVS and CAD have been described in detail elsewhere [19]. Interestingly, an isolated CAD occurred in only 8/31 patients with CAD in our cohort, while the other patients presented with multiple CAD without other complications in five cases, and with concomitant complications including SAH, PRES, ICH, and IS in 18 cases. Hypotheses to explain the link between RCVS and CAD have been discussed before [19,20]. Possibly, patients presenting with both conditions carry an underlying susceptibility favoring an atypical clinical presentation without TCH, and the co-occurrence of RCVS, CAD, and additional complications. It needs to be elucidated if this clinico-radiological variant might be related to an aberrant trigeminovascular reflex with inadequate secretion of CGRP as discussed above.

The exploration of other risk factors for neurological complications in RCVS was not the main objective of this study. In brief, these other risk factors included, in the order of their strength of association, postpartum status, female sex, a history of anxiety or depression (but not use of serotonergic antidepressants), blood pressure surge during RCVS, and older age, with an increase in the odds of complications by 4% per each 1 year. Nevertheless, severity of postpartum RCVS might be overestimated due to underreporting of pure cephalalgic forms.

To date, only one study has addressed the role of gender and hormonal influences in RCVS [21]. Whereas women with RCVS presented more often with infarcts and clinical worsening than men, the risk was not significantly different between premenopausal, postmenopausal, and postpartum women. Likewise, research on migraine has shown a higher risk for IS in women than in men [22]. Interestingly, experimental studies indicate that sex hormones may modulate CGRP receptor synthesis, expression, or release in the trigeminovascular system, and CGRP levels vary between men and women and depending on hormonal status [23].

While prior serotonergic antidepressant use predicted clinical and angiographic worsening in one study [8], a history of anxiety or depression has not been described as a risk factor for complications. However, the prevalence of psychiatric history was not reported by the majority of studies on RCVS.

Blood pressure surge might favor complications (e.g., PRES) or arise as a consequence of complications (e.g., IS).

Up to now, age has not been described as a risk factor for complication in RCVS. It would be interesting to further examine a possible clinico-radiological variation of RCVS dependent on age.

Our study included patients from three cohorts, of which two have not been published before. Heterogeneity between those cohorts is most likely explained by, first, the prospective versus retrospective design. More precisely, the prevalence of all comorbidities (e.g., migraine and depression) was highest in cohort A, since a careful interview was systematic as opposed to a mostly pragmatic interview in clinical routine. Secondly, cohorts A and B were recruited mainly by neurologists specializing in headache disorders, and cohort C mainly by vascular or general neurologists. A more detailed interview on premorbid headache disorders might explain the significantly higher prevalence of migraine in cohort A/B.

Strengths of our study include the relatively large number of patients, a prospective study design for one half of our cohort, and recruitment from one emergency headache clinic and two neurological wards, possibly balancing the selection bias for milder cephalalgic versus more severe forms of RCVS, respectively.

Limitations include the retrospective data acquisition for cohort B/ C. Although the type of headache at onset was documented at onset and not retrospectively, we considered a misclassification bias which was refuted by a sensitivity analysis on cohort A. Of the 345 patients, six patients woke up with a headache of maximum intensity. In these patients, the real type of onset remains unknown. Further, the group of patients without TCH at onset was heterogeneous, ranging from severe headache to absence of headache. Our study included patients from two French hospitals, and the external validity of our results remains unclear. The results of the largest cohort studies on RCVS from Japan, Korea, Taiwan, Italy, and France point to substantial differences between Asian and European patients. Thus, further studies need to examine if our findings are also true for other populations. Finally, we documented the occurrence of a neurological deficit and radiological lesions, but we did not evaluate clinical or radiological severity by a specific score. Scores for the clinical severity of RCVS and for the severity of parenchymal lesions have not been proposed to date, while a score for the evaluation of the severity of vasoconstriction has been suggested by Chen et al. [24].

CONCLUSIONS

Our results indicate that absence of TCH at onset might predict a higher risk of complications in RCVS. This underlines the necessity of considering the diagnosis of RCVS even in the absence of severe headache. Further multicentric studies are warranted in order to prove this finding, allowing for better pathophysiological understanding and clinical management of patients with RCVS.

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CONFLICT OF INTEREST

JM received travel, accommodation, and meeting expenses from SOS Oxygène, Amgen, Novartis, Elsevier, and Homeperf and received honoraria for advisory boards or speaker fees from Teva, Lilly, and Novartis not related to the submitted work; he is a member of the redaction committee of "La Lettre du Neurologue"

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AUTHOR CONTRIBUTIONS

Kristin Sophie Lange: Conceptualization (supporting); Data curation (equal); Formal analysis (lead); Investigation (supporting); Methodology (equal); Project administration (supporting); Resources (equal); Visualization (lead); Writing-original draft (lead); Writing-review & editing (equal). **Ophélie Forster:** Conceptualization (supporting); Data curation (equal); Investigation (supporting); Resources (equal); Writing-review & editing (equal). **Jérôme Mawet:** Data curation (equal); Investigation (supporting); Project administration (supporting); Resources (equal); Writing-review & editing (equal). **Gabrielle Tuloup:** Data curation (equal); Investigation (supporting); Resources (equal); Writing-review & editing (equal). **Cécilia Burcin:** Investigation (supporting); Resources (equal); Writing-review & editing (equal). **Lucas Corti:** Investigation (supporting); Resources (equal); Writing-review & editing (equal). **Claire Duflos:** Formal analysis (supporting); Methodology (equal); Resources (equal); Visualization (supporting); Writing-review & editing (equal). **Caroline Roos:** Investigation (supporting); Project administration (supporting); Resources (equal); Writing-review & editing (equal). **Anne Ducros:** Conceptualization (lead); Data curation (equal); Investigation (lead); Methodology (equal); Project administration (lead); Resources (equal); Supervision (lead); Writing-review & editing (equal).

DATA AVAILABILITY STATEMENT

In line with national confidentiality requirements, the data that support the findings of this study are available from the corresponding author upon reasonable request. Due to privacy restrictions, the data will be anonymized before sharing.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.