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Intra-arterial application of nimodipine in reversible cerebral vasoconstriction syndrome: A diagnostic tool in select cases?

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Abstract

Introduction: Differential diagnoses of the reversible cerebral vasoconstriction syndrome (RCVS) include all forms of intracranial stenotic disease, such as primary or secondary vasculitis of the central nervous system. Here, we tested the hypothesis that angiographic response to intra-arterial nimodipine application may be helpful in differentiating between RCVS and other entities.

Methods: A digital subtraction angiographic (DSA) series of nine consecutive patients with suspected RCVS that were treated by intra-arterial nimodipine due to clinical worsening were retrospectively analyzed. Pre- and post-therapeutic DSA findings of patients with later-confirmed RCVS were compared to those in which another diagnosis was finally made.

Results: Intra-arterial nimodipine resulted in a normalization of both the diameter of the main trunks of the cerebral vessels and the caliber of the peripheral vessels in all RCVS patients. This was not the case in the non-RCVS patients, in whom only a slight general vasodilatation was observed.

Discussion: Our preliminary results indicate that angiographic response to intra-arterial application might be a helpful differential diagnostic tool in select patients with suspected RCVS.

Keywords

Reversible cerebral vasoconstriction syndrome, RCVS, nimodipine, vasculitis, PACNS

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Introduction

Reversible cerebral vasoconstriction syndrome (RCVS) indicates a specific complex of clinical and imaging findings, namely, (i) severe headache with or without additional focal neurological symptoms or seizures, (ii) angiographic evidence of cerebral vasoconstriction and (iii) reversibility of the vessel abnormalities within less than three months (1). Although a wide variety of predisposing factors has been identified, the most common of which are pregnancy or recent childbirth and the use of vasoactive substances, in over one-third of cases no trigger can be identified (1,2).

RCVS has a benign clinical course in the wide majority of cases. Yet severe complications have been described, including subarachnoid hemorrhage (SAH), ischemic cerebral infarction, intracerebral hemorrhage and even death (1–5). Thus far, therapeutic strategies in those patients with a more malignant course lack clear evidence (1). On the basis of treatment of vasospasm in SAH (6), some authors suggest nimodipine, which can be applied orally, intravenously or even intra-arterially (7–11). The last application in clinically progressive RCVS has been described in single case reports (9–11).

During the early course of RCVS, differential diagnoses include all forms of intracranial stenotic disease, such as primary or secondary vasculitis of the

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central nervous system, Moya-Moya disease or atherosclerotic disease (1,3,12,13), especially because in the majority of these diseases headaches are also one of the leading symptoms. Angiographic response after intra-arterial nimodipine application may be different between these entities. To test this hypothesis, we retrospectively analyzed all consecutive patients at our institution who were treated with intra-arterial nimodipine due to clinical worsening in suspected RCVS. Specifically, radiological and clinical response of patients with later confirmation of RCVS was compared to the response of those in which another final diagnosis was made.

Methods

Patients and diagnoses

Since 2008, we have used intra-arterial nimodipine as an escalating treatment option in patients with suspected RCVS and clinical deterioration. To identify all eligible patients for the retrospective case series present here, we searched our electronic neuroradiological database to identify all patients between January 2008 and June 2010 in which intra-arterial nimodipine had been applied for any reason. Patients who had received intra-arterial nimodipine for vasospasm due to aneurysmal SAH and patients with iatrogenic vasospasm due to mechanical irritation during diagnostic or interventional digital subtraction angiography (DSA) were excluded from further analysis. Inclusion criteria were (i) clinical presentation typical for RCVS with severe headache with or without additional focal neurological symptoms or seizures, (ii) MR angiographic evidence of multifocal irregularities of the cerebral vessels, and (iii) follow-up examinations including MR angiography or DSA performed within three to six months from symptom onset.

Clinical records, laboratory and histological findings, as well as all available imaging data sets (MRI and DSA) including all follow-up examinations of the patients matching these criteria, were reviewed by both an experienced neurologist and a neuroradiologist in consensus in order to verify the definite diagnosis.

DSA and intra-arterial nimodipine therapy

Diagnostic DSA and consecutive intra-arterial application of nimodipine were performed on a biplanar DSA unit with an image matrix of 1024×1024 (Neurostar, Siemens Medical Solutions, Germany) using a saline-flushed guide catheter under systemic heparin therapy. After a diagnostic series of both internal carotid arteries (ICAs) and the dominant vertebral artery (VA), the catheter was placed in the ICA on the most affected side or in the dominant VA if the posterior circulation was involved. In cases with severe vasoconstrictions in more than one territory (both ICA territories, and/or posterior circulation), a second and—in one case—a third coaxial system were introduced to allow for simultaneous application of the drug. Intra-arterial nimodipine was applied in a total dosage of 0.5 to maximal 2 mg/hour for a maximum of 2.5 hours. The whole procedure was performed under anesthesiological standby with continuous monitoring of systemic blood pressure, heart rate, respiratory frequency and arterial oxygen saturation. At the end of the procedure, intra-arterial infusion of nimodipine was stopped, and replaced in the case of documented radiological response by intravenous (IV) application at a maximum rate of 2 mg/hour.

Image interpretation and data analysis

DSA series pre– and post–intra-arterial application of nimodipine were analysed by two experienced neuroradiologists in consensus, who were blinded with regard to the patients' definite diagnoses. First, readers analyzed the initial series for signs of vasoconstriction and the presence of stenosis to determine the predominantly affected vessels. For the main trunks of the large cerebral arteries (distal segment of the ICAs, M1 segment of the middle cerebral arteries [MCAs], A1 and A2 segments of the anterior cerebral arteries [ACAs], P1 segment of the posterior cerebral arteries [PCAs] and the basilar artery [BA]), the punctum maximum of the vasoconstriction or stenosis was identified and considered as region of interest (ROI) for further analysis. To determine the effect of nimodipine afterward, readers (i) measured the diameters of the main trunks of the affected large cerebral arteries at the respective ROI and (ii) visually analyzed the peripheral segments of these arteries for the presence of lumen irregularities in both the pre- and the post-therapeutic series. With regard to the main trunks, differences between pre- and post-interventional diameters were calculated. The mean value of the differences measured in all vessels in RCVS patients was compared to that observed in the non-RCVS group.

Results

Patients and diagnoses

Nine patients (seven females, mean age = 42 years, range = 32–60 years) matched the inclusion criteria. Five of these patients (five females, mean age = 41.6 years, range = 32–50 years) were definitely diagnosed with RCVS based on follow-up MRA imaging after three to six months showing complete resolution of

the vessel abnormalities. The remaining four patients suffered from primary angiitis of the central nervous system (PACNS; $N=1$); Moya-Moya disease ($N=2$) and arteriosclerotic stenosis ($N=1$). The diagnosis of PACNS was proven by autopsy. Moya-Moya disease and arteriosclerosis were diagnosed based on stable or progressive MRA findings on three-to-six months' follow-up. Two of the RCVS cases (patient 1 and patient 4) have been published previously as case reports (9,10). For details on demographic, clinical and outcome patient information see Table 1. Table 2 summarizes the MRI findings.

DSA findings and intra-arterial nimodipine therapy

Intra-arterial nimodipine was applied for 1–2.5 hours in the left ICA in two cases, in the right ICA in three cases and in both ICAs in four cases. In one of these cases, nimodipine was also infused into the VA (patient 4). It was applied via one catheter in five cases, simultaneously via two catheters in three cases, and simultaneously via three catheters in patient 4. Intra-arterial therapy was repeated on day 2 in two cases (one RCVS case, and one non-RCVS case) (for details, see Table 3). Intra-arterial application of nimodipine was well tolerated by all patients.

Nimodipine resulted in a normalization of both the diameter of the main cerebral vessels and the caliber of the peripheral vessels in all RCVS patients (Figure 1). The mean difference in pre- and post-therapeutic vessel diameter measured in the ROIs was $7.1\,\text{mm} \pm 1.5\,\text{mm}$ in these patients. There was also a normalization of the multifocal segmental vasoconstriction of the peripheral segments in RCVS cases. In the non-RCVS patients, a slight general vasodilatation of the peripheral vessels was visually observed while there were no relevant measurable diameter changes detectable within the ROIs (mean difference $= 0.0\,\text{mm} \pm 0.3\,\text{mm}$) (Figure 2; Table 3).

Table 1. Demographic and clinical patient data and outcome

Patient Nb.	Sex/age	Final diagnosis#	Clinical sympons at initial presentation	New or progressive clinical symptoms warranting i. a. nimodipine therapy	Outcome (mRS after 3 months)
1*	f/32	RCVS (postpartum)	headache, hemianopsia to left side, seizures	right arm paresis	0
2	f/50	RCVS	headache, disorientation,	left hemiparesis, hemineglect	3
3	f/40	RCVS	headache, cortical blindness, disorientation,	gaze palsy, dysarthria, right hemiparesis, left facial palsy	2
4*	f/50	RCVS	headache	disorientation, mnestic deficits	1
5	f/36	RCVS (hormone therapy)	headache, disorientation	right inferior quadrant anopsia	0
6	m/38	Moyamoya Disease	headache, hypesthesia, dysarthrophonia	transient left hemiparesis	0
7	f/36	Atherosclerosis	headache, paresthesia	left arm paresis, paresthesia	0
8	f/60	PACNS	headache	right hemiparesis, aphasia	6 (brain death)
9	m/36	Moyamoya Disease	headache, fluctuating left hemihypesthesia	hemiparesis, dysarthria	0

Abbreviations in alphabetical order: f: female; i. a.: intra-arterial; ICA: internal carotid artery; m: male; MCA: middle cerebral artery; mRS: modified Rankin Scale; Nb: number;
PACNS: primary angiitis of the central nervous system; RCVS: reversible cerebral vasoconstriction syndrome.
*: These cases have been previously reported as case reports (9,10).
#: Predisposing factors are given in parenthesis (if applicable).

Table 2. Imaging findings

Patient Nb.	Diagnosis	Complications on MRI and CT	
		Acute ischemia (localization)	Hemorrhage (localization)
1*	RCVS	+ (borderzones, bilaterally)	SAH (right cortical)
2	RCVS	+ (both MCA and both ACA territories)	SDH (right frontal)
3	RCVS	+ (borderzones, bilaterally; left MCA territory)	SAH (right cortical)
4*	RCVS	+ (left borderzone; both PCA and left MCA territories)	–
5	RCVS	+ (left ACA, both MCA and PCA territories)	SAH (right cortical)
6	Moyamoya Disease	– –	–
7	Arteriosclerosis	+ (right MCA territory)	SAH (right cortical)
8	PACNS	+ (left MCA and left ACA territory)	–
9	Moyamoya Disease	+ (right MCA territory)	–

Abbreviations in alphabetical order: ACA: anterior cerebral artery; MCA: middle cerebral artery; Nb.: number; PACNS: primary angiitis of the central nervous system; PCA: posterior cerebral artery; RCVS: reversible cerebral vasoconstriction syndrome; SAH: subarachnoidal hemorrhage; SDH: subdural hemorrhage.
*: These cases have been previously reported as case reports (9,10).

Discussion

The imaging hallmark of RCVS is a typical ''string and beads'' appearance of the involved cerebral arteries. In most patients, these typical findings can be demonstrated by MR or CT angiography. DSA is not required as a standard diagnostic tool in RCVS (1). At symptom onset, other neurological disorders presenting with headache and cerebral arterial vasoconstriction, first of all primary or secondary vasculitis of the central nervous system, represent the major differential diagnoses (1,10). The differentiation of RCVS from other entities with cerebral-vessel narrowing represents a diagnostic challenge for both clinicians and neuroradiologists, especially in patients in which the typical precipitating factors are lacking, and who present with atypical headache forms. Whereas the sensitivity of diagnostic angiographic methods in RCVS is very high, it lacks specificity, and RCVS can easily be mistaken for PACNS even on DSA series (12). The situation is complicated by the fact that histological signs of secondary inflammation have been found in select patients with dramatic RCVS and prolonged diffuse vasospasm (14). Thus, per definition, the definite diagnosis of RCVS can only be made by follow-up imaging, demonstrating the normalization of the vessel diameter after three months (1).

Yet, the distinction between RCVS and vasculitis or arteriosclerotic disease is of considerable therapeutic relevance: while steroids or cytotoxic drugs are the treatment of choice in vasculitis, they should be avoided in RCVS (1,3). Therefore, a diagnostic tool for the differentiation of both entities early in the clinical cause would be desirable.

There exist no large clinical trials on the adequate treatment of RCVS. Small case series indicate that calcium channel blockers such as nimodipine—applied orally or intravenously—seem to be the best therapeutic option (3,7,8,14,15). Yet, determination of the real benefit of this approach on outcome cannot be easily obtained, considering the usually benign, self-limiting course of RCVS.

However, a small subset of RCVS patients shows clinical deterioration despite the above-mentioned treatment. Complications include ischemic stroke (in 7–31%) (1–4,16), intracranial hemorrhage (in 14–25%) (2–4), convexity SAH (in 22 %) (1) and even death (4,5).

In patients with severe vasospasm secondary to an aneurysmal SAH, intra-arterial application of nimodipine has been shown to be a safe and effective endovascular therapeutic option in select cases (6,17,18). Based on these experiences, this therapeutic option has been successfully applied in a limited number of RCVS cases (9–11). At our institution, we use intra-arterial nimodipine application as an escalating treatment option in patients with suspected RCVS and clinical deterioration despite IV nimodipine treatment. In all RCVS patients, we have observed prompt resolution of vasoconstriction with elimination of the ''string and beads'' vessel appearance not only on the side of drug application but also on the contralateral side if application was only done unilaterally. This reveals a strong systemic effect of intra-arterial nimodipine in RCVS patients. Our observation provides further support for the hypothesis that the etiology underlying the vessel narrowing in RCVS is vasospasm, comparable to that observed in SAH (11).

Table 3. DSA findings and endovascular intervention details and results

Patient No.	Diagnosis	Predominantly affected vessels on DSA	Time from symptom onset to i. a. nimodipine application (d)	Site of i. a. nimodipine application	Dose (mg/h)	Duration of application (h)	Mean difference in vessel diameter pre-versus post i.a. nimodipine (mm ± SD)
1*	RCVS	both ACA, MCA, PCA	3	Left ICA	2.0	1	0.8 ± 0.2
2	RCVS	left MCA, PCA, both ACA	3	Left ICA§	1.0	1	0.6 ± 0.5
				Right ICA§	1.0	1	
			4	Left ICA	1.5	0.5	0.6 ± 0.4
				Right ICA	1.5	0.5	
3	RCVS	both ACA, MCA, PCA	1	Left ICA§	0.5	0.5	0.9 ± 0.1
				Left ICA§	1.0#	0.5	
				Right ICA§	0.5	0.5	
				Right ICA§	1.0#	0.5	
4*	RCVS	both ACA, MCA, PCA, BA	17	Left ICA§	1.0	0.5	0.8 ± 0.3
				Right ICA§	1.0	1	
				VA§	1.0	1	
5	RCVS	both ACA, MCA, PCA	7	Left ICA	2.0	0.5	0.4 ± 0.2
				Right ICA	2.0	0.5	
6	Moyamoya Disease	both MCA	8	Right ICA	1.0	1	0.0 ± 0.1
7	Atherosclerosis	right MCA	11	Right ICA	2.0	1.5	0.0 ± 0.1
8	PACNS	left ICA, ACA, MCA	4	Left ICA	2.0	1.5	0.0 ± 0.1
			5	Left ICA	2.0	2.5	0.0 ± 0.1
9	Moyamoya Disease	right ICA, MCA, A. ophthalmica	20	Left ICA	1.0	1	0.0 ± 0.1

Abbreviations in alphabetical order: ACA: anterior cerebral artery; BA: basilar artery; DSA: digital subtraction angiography, i. a.: intra-arterial; ICA: internal carotid artery; MCA: middle cerebral artery; PACNS: primary angiitis of the central nervous system; PCA: posterior cerebral artery; RCVS: reversible cerebral vasoconstriction syndrome; SD: standard deviation.

*: These cases have been previously reported as case reports (9,10).

#: 0.5 hours after onset of i. a. nimodipine, dosage was increased from 0.5 mg/h to 1 mg/h.

§: simultaneous application of i. a. nimodipine via two or three catheters.

On the contrary, in the non-RCVS cases in which follow-up revealed other etiologies of vessel narrowing, the focal stenoses were widely preserved on post-therapeutic images. Thus, the presence or absence of an effect of intra-arterial nimodipine in patients with cerebral vessel narrowing might be an important diagnostic tool to differentiate RCVS from other, non-reversible stenotic disorders.

Comparable to IV and per os application, intra-arterial application of nimodipine was well tolerated by all patients. The major caveat is a decrease of systemic blood pressure due to the vasodilatative effect of the drug (9,10). Therefore, anesthesiological standby is required to ensure continuous blood pressure control and quick appropriate treatment if necessary to avoid the danger of cerebral hypoperfusion in the presence of fixed arterial stenosis. In general the blood pressure–lowering effect of intra-arterial nimodipine is less than the effect of long-term IV nimodipine. In addition, general complications of intra-arterial catheterization,

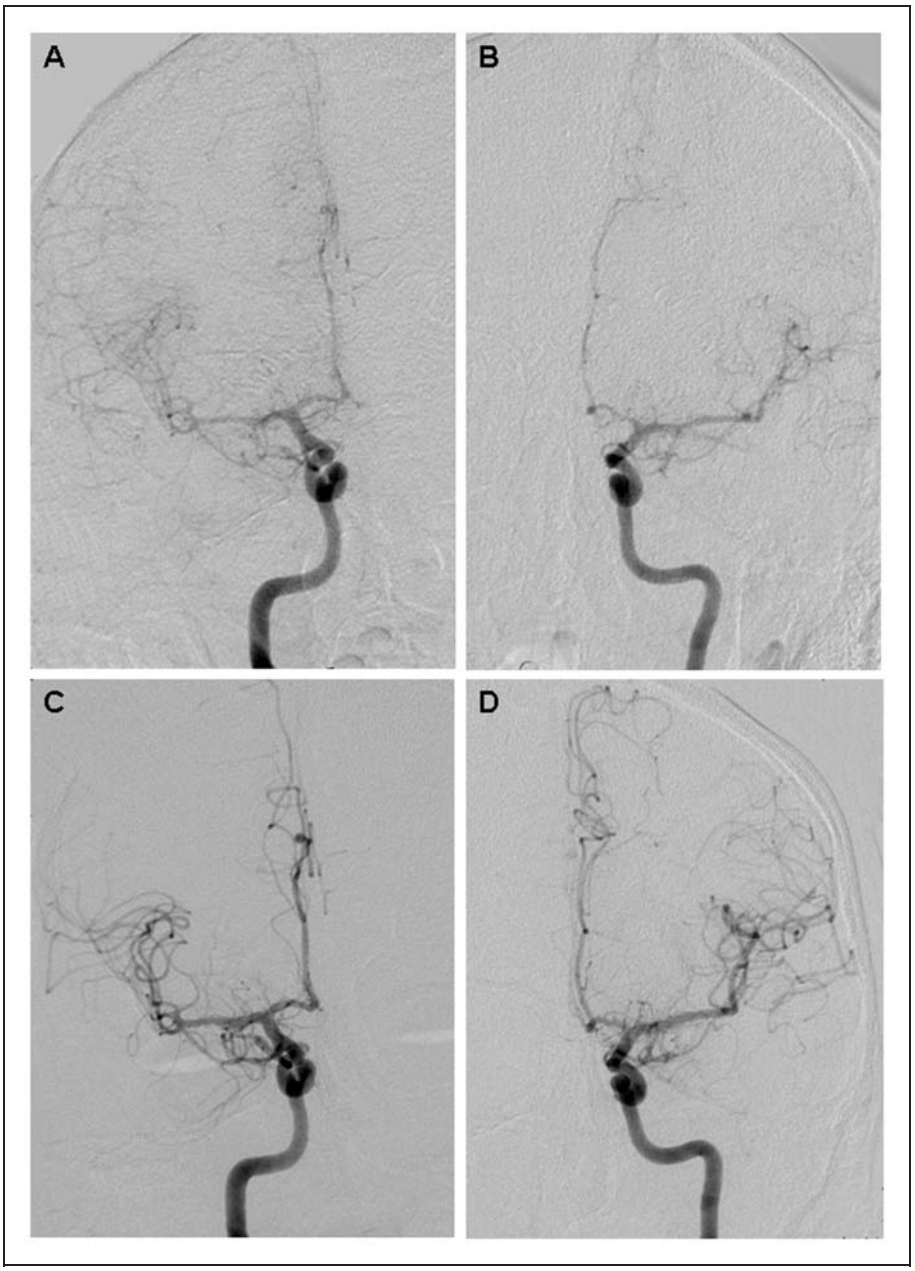

Figure 1. Effect of intra-arterial nimodipine on vessel diameter in RCVS patients. Digital subtraction angiography (DSA) images of the right (A and C) and left (B and D) internal carotid artery (ICA) in a 40 year-old patient with RCVS (patient 3). Initial images (A and B) reveal severe vasoconstrictions of the M1, A1 and A2 segments and of the peripheral vessels bilaterally. DSA series performed after intra-arterial application of nimodipine (C and D) show a normalization of the vessel diameter of both the main trunks and of the peripheral vessels. Nimodipine was infused simultaneously via two catheters—one in each ICA—or a total of one hour. At 0.5 hours after onset of intra-arterial nimodipine, dosage was increased from 0.5 mg/hour to 1 mg/hour.

such as vessel dissection and the potential risk of reperfusion injury, have to be considered (11). Regarding these drawbacks and the usual benign course of RCVS, it must be emphasized that most patients with suspected RCVS can be diagnosed by MR or CT angiography alone, and that diagnostic DSA and especially intra-arterial nimodipine treatment are only indicated in a small proportion of patients with progressive disease.

The retrospective design and the small number of cases represent limitations of the study. Due to these limitations, our results do not prove that angiographic non-responsiveness rules out RCVS, and we cannot definitely determine whether the angiographic response

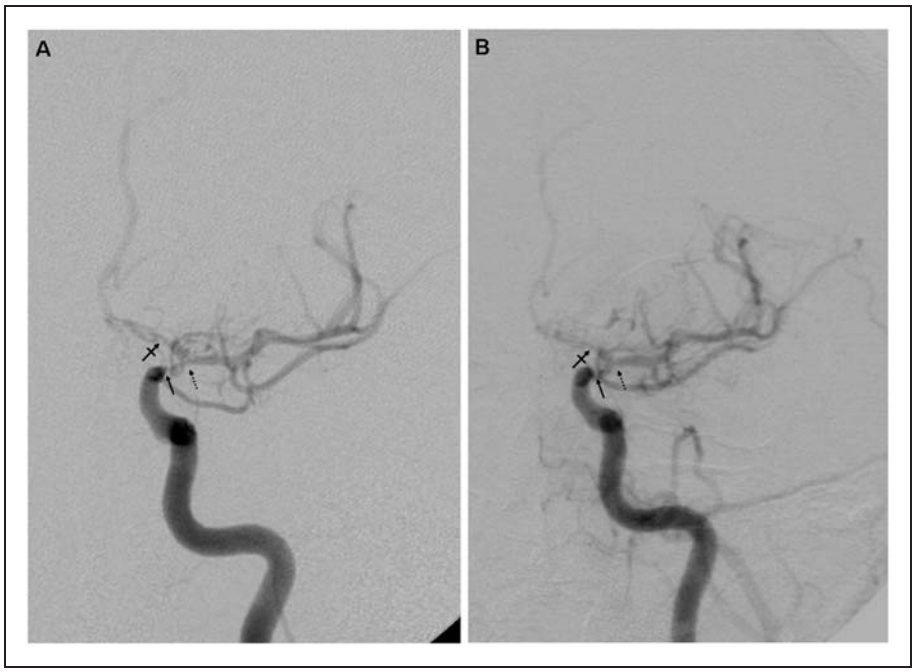

Figure 2. No measurable effect of intra-arterial nimodipine in non-RCVS patients. Digital subtraction angiography (DSA) images of the left internal carotid artery (ICA) in a 60-year-old female patient with primary angiitis of the central nervous system (PACNS; patient 8) performed before (A) and after (B) intra-arterial application of 2 mg/hour nimodipine for 1.5 hours via the left ICA. Comparing the pre- (A) and post-therapeutic series, there are no measurable changes in the diameter of the affected main trunks (distal ICA, normal arrow; proximal M1-segment, dotted arrow; and A1-segment, crossed arrow).

is long-lasting or only transient in nature (11). Further prospective studies are needed to definitely confirm our hypothesis.

Conclusion

Our observations further support the theory that vasospasm is the major pathomechanism of RCVS. Furthermore, our results indicate that intra-arterial nimodipine might be useful as a diagnostic tool in patients with headaches and suspicious cerebral angiographic findings, in which differentiation between RCVS and PACNS or other stenotic diseases is mandatory but cannot be achieved otherwise because of equivocal clinical and laboratory findings. These preliminary findings have to be confirmed prospectively in a larger series of severe cases with suspected RCVS and progressing symptoms.

Acknowledgement

J Linn and G Fesl contributed equally to this study.

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