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ORIGINAL COMMUNICATION

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Reversible cerebral angiopathy

Efficacy of nimodipine

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Abstract Reversible cerebral angiopathy (RCA) is responsible for disabling headache and potential stroke complications. Most patients respond poorly to analgesics. We describe four patients with typical RCA whose headache rapidly disappeared after IV nimodipine treatment was initiated.

Key words cerebral angiopathy · vasospasm · stroke · nilmodipine

Introduction

Reversible cerebral angiopathy (RCA) is characterized by severe headaches associated with diffuse segmental stenoses of the medium-sized cerebral arteries due to vasospasm, completely reversible within weeks to months [1]. Although prognosis is usually good, life-threatening complications may occur, including hemorrhagic and ischemic stroke [9]. There is no known specific treatment and numerous analgesics are usually delivered with the intention to relief headaches. Isolated case reports have suggested that nimodipine could improve headache in patients with well-defined RCA [7, 10]. We here report our experience on efficacy of nimodipine in four RCA patients.

Patients and methods

Patients

From 2002 to 2004, 4 patients with severe diffuse headache due to RCA were admitted in our department. Onset was hyperacute in 3 patients taking the form of a thunderclap headache, and was subacute (several hours) in 1 patient. Demographic and clinical data are summarized in the Table. The diagnosis of RCA was based on cerebral angiography with a typical appearance of multiple and diffuse segmental stenoses on the medium-sized arteries. In all patients, follow-up MRA 1 to 3 months after headache resolution showed complete resolution of intracranial artery abnormalities (Figure). All patients also had cerebral MRI (T1, T2, FLAIR and DWI sequences) with intracranial MRA and transcranial Doppler (TCD) sonography at admission. Abnormalities on MRA were in agreement with those observed on angiography. A small intracerebral hemorrhage was observed in Patients 2, 3 and 4 but blood did not spread to the subarachnoid

Table Patients characteristics and nimodipine protocols

Patient - Age(years)/sex	Trigger	Clinical history before nimodipine treatment	Cerebral lesions	Initial nimodipine protocol (duration)	Response to nimodipine treatment and evolution
1 - 29/M	Coïtus	TCH + 5-d headaches	None	IV 1 mg/h (6 days) No switch to per os	Headache relief within 6 hours Moderate recurrence after treatment disruption Per os 240 mg/d for 10 w (gradual tapering) No other recurrence
2 - 50/F	Acute hypertension (disruption of treatment)	4-d headaches and vomiting	L occipital hemorrhage	360 mg/d per os (8 days)	Headache partial relief but secondary worsening 7-d IV 1–2 mg/h. Headache relief within 3 hours Switch to per os 270 mg/d for 12 w (gradual tapering) No recurrence. Residual partial epileptic seizures
3 - 55/F	Recent treatment with paroxetine	TCH + 10-d headaches and vomiting R hemianopsia	L occipital hemorrhage	IV 1 mg/h (8 days)	Headache relief within 24 hours Switch to per os 240 mg/d for 7 w (gradual tapering) No recurrence. No neurological sequellae
4 - 52/F	Acute stress	TCH + 10-d headaches and vomiting	R frontal hemorrhage	IV 1 mg/h (10 days)	Headache reduced within 6 hours with persistent headache during 4 days. Switch to per os 360 mg/d for 4 w (gradual tapering) No recurrence. No neurological sequellae

d = day; IV = intravenous; L = left; R = right; TCD = transcranial Doppler; TCH = thunderclap headache; w = weeks

space on FLAIR sequences. Laboratory tests including standard blood tests, immunological investigations and CSF study were all normal or negative.

Treatment

During the first days after admission, the four patients received various analgesics including non steroid anti-inflammation agents, paracetamol, dextropropoxyphen and morphin. None of these treatments led to sustained improvement of headache. Patients 1 and 3 even reported worsening of headache, which was qualified as "worst ever". Therefore, treatment with nimodipine was decided upon.

Results

Nimodipine was initiated 4 to 10 days after onset of the headache. Intravenous (IV) nimodipine was initially administered at 1 mg/h in 3 patients. Patient 2 first received oral nimodipine (360 mg/d) and IV nimodipine 8 days later because of headache worsening. Clinical response to IV nimodipine was dramatic in the four patients, with headache relief within a few hours. Patient 4 still complained of mild headaches during the 4 days after induction, although she acknowledged notable improvement short after initiation. Patient 1 was discharged after 6 days of IV nimodipine with no switch to the oral form. Moderate headache recurred within the 24 hours after nimodipine withdrawing and oral nimodipine was introduced one week later for 10 weeks. In Patients 2, 3, and 4, IV nimodipine was switched to oral nimodipine (240–360 mg/d) and gradually tapered (7 to 12 weeks). There was no recurrence. Details of the nimodipine protocol are provided in the Table. Blood pressure was monitored in all patients. In Patient 2, stabilization of acute hypertension was observed under treatment. In the 3 other patients, we did not observe significant lowering of blood pressure.

In all patients, pre-treatment transcranial Doppler (TCD) sonography showed marked elevation of blood flow velocity (BFV) (peak flow values >120 cm/s) in at least one middle cerebral artery (MCA). In Patient 2, whose headache was reinforced under oral nimodipine, peak flow in the right MCA reached 260 cm/s before IV nimodipine infusion was started. Early repeat of TCD sonography was obtained for Patients 2, 3 and 4 within 5 to 8 days. Improvement of BFV was observed with a 20–25% reduction in the MCA peak flow. In all patients, follow-up TCD sonography at 1 month was normal.

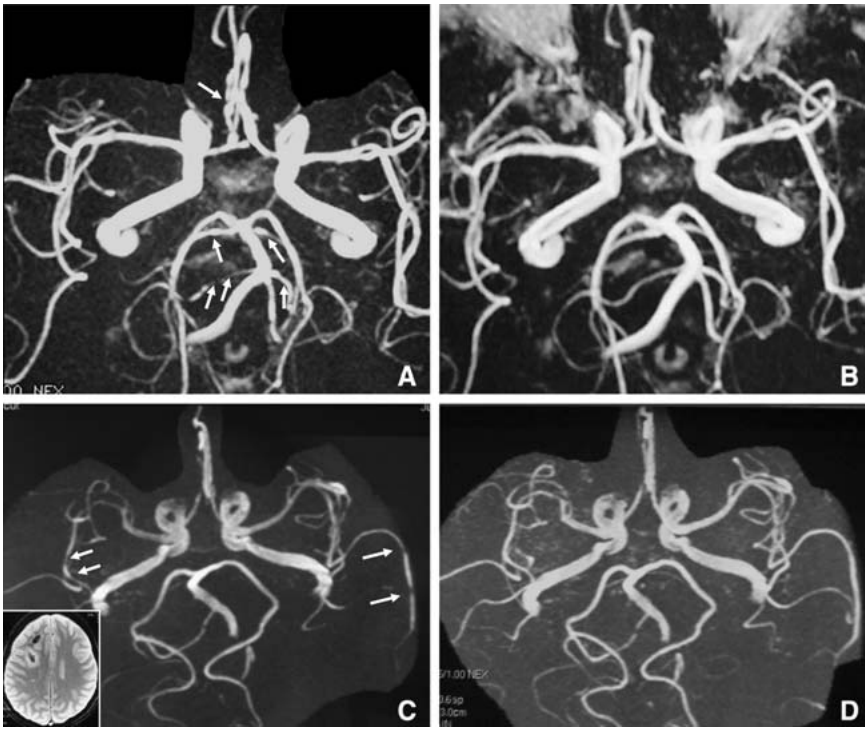

Fig. (Top) Patient 1. **A** Initial MR angiography (MRA) showing multiple segmental stenoses on cerebellar and anterior cerebral arteries (arrows). **B** Follow-up MRA at one month was normal. (Bottom) Patient 3. **C** Initial MRI/MRA showing a small right frontal hemorrhage (gradient-echo T2*-weighted sequence) and segmental stenoses on both middle cerebral arteries (arrows). **D** No more abnormality was present on MRA one month later

Discussion

We observed an impressive headache relief in four patients with RCA shortly (i.e. a few hours) after IV nimodipine was initiated. Before this report, efficacy of nimodipine was tested in 2 patients with well-defined RCA. Sturm et al. [10] first reported a 58 year-old woman with RCA revealed by thunderclap headache and complicated by posterior ischemic infarct. Improvement occurred in a few days after IV nimodipine was initiated (dose not indicated) and switched to oral nimodipine after 3 days. More recently, Nowak et al. [7] reported a 63 year-old woman with thunderclap headache and a typical radiological pattern of RCA. Eleven days after onset of the headache, the patient's condition deteriorated, due to bilateral hemispheric infarcts. Headache even worsened during hospitalisation, while the patient was receiving oral steroids and oral nimodipine (200 mg/d). IV nimodipine (2 mg/h) was started and headache improved a few hours later.

Efficacy of nimodipine was also reported in 3 patients with severe headaches and intracranial vasospasms, under the appellation of primary thunderclap headache [4] or bath-related headache [4, 6]. In fact, the diagnosis of RCA can be confidently made in these cases. Liao et al. [4] reported a 51 year-old-woman with an acute bath-related headache. It was only partially responsive to oral nimodipine (360 mg/d) while IV nimodipine (0.5–1 mg/h) relieved pain within several hours. Lu et al. [5] reported a 46-year-old woman with thunderclap headache who partially responded to oral nimodipine (360 mg/d) but headache disappeared under IV nimodipine (2 mg/h) treatment. Finally, Mak et al. [6] described a 50-year-old woman with bath-related headache for whom oral nimodipine (360 mg/d) seemed to shorten duration of the headache. IV nimodipine (48 mg/d) was also delivered in two young women with postpartum RCA who rapidly improved [3].

Our observations confirm and amplify these previous reports. The close chronological concordance between headache relief and initiation of the nimodipine infusions was in favor of a direct therapeutic effect. According to such findings, we suggest that : 1) nimodipine could be effective for headache relief in RCA patients, whatever the headache characteristics are; 2) nimodipine could be more effective when delivered in the IV than the oral form, possibly because of differences in bioavailability; 3) gradual tapering of the treatment should be recommended over several weeks in order to prevent recurrence. Close follow-up of the arterial pressure is required during treatment since systemic hypotension could precipitate cerebral ischemia in RCA patients with severe intracranial vasospasm [5]. We, however, did not observe any side effect of IV nimodipine in our RCA patients.

The mechanism by which nimodipine dramatically improves headaches in RCA patients remains unclear

[2]. Close relationship between IV nimodipine induction and BFV improvement on TCD sonography has suggested some direct pharmacological intervention on the vasospasms [7]. Indeed, oral nimodipine is currently recommended in aneurysmal subarachnoid hemorrhage in order to prevent vasospasm [8]. The effect of the drug is attributed to the relaxation of the smooth muscle of arterial blood vessel walls. However, the clinical effect of nimodipine in RCA probably does not result from vasospasm removal only since the drug improved thunderclap headache in some patients without arterial abnormalities [4–6]. Interestingly, oral nimodipine was sufficient to improve headache in such patients free of vasospasm.

Whether early nimodipine treatment could protect RCA patients from stroke complications remains to be settled, but considering the dramatic clinical improvement repeatedly reported with the drug, it should be considered in RCA patients with intractable headache at the acute phase. Properly designed therapeutic trials are required to confirm the benefit of nimodipine in this condition.

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