

Reversible segmental cerebral vasoconstriction (Call–Fleming syndrome): are calcium channel inhibitors a potential treatment option?

DA Nowak, SO Rodiek¹, S Henneken, J Zinner, R Schreiner, H-H Fuchs & H Topka

Department of Neurology and Clinical Neurophysiology and ¹Department of Radiology, Academic Hospital München Bogenhausen, Technical University of Munich, Munich, Germany

Cephalalgia

Nowak DA, Rodiek SO, Henneken S, Zinner J, Schreiner R, Fuchs H-H & Topka H. Reversible segmental cerebral vasoconstriction (Call–Fleming syndrome): are calcium channel inhibitors a potential treatment option? *Cephalalgia* 2003; 23:218–222. London. ISSN 0333-1024

The Call–Fleming syndrome is characterized by sudden onset of thunderclap-like headache and focal neurological deficits. The pathophysiological correlate is a reversible segmental cerebral vasoconstriction frequently associated with focal cerebral ischaemia. The syndrome has been described in a variety of clinical conditions, and recently an association between the syndrome and exposure to vasoactive drugs was observed. Effective treatment options are not known. A 63-year-old female developed sudden ‘worst ever’ headache. Initial neurological examination, laboratory blood tests, CSF examination and brain magnetic resonance imaging (MRI) were normal. Previous medical history was unremarkable and she did not take vasoactive drugs. Eleven days after the onset of headache she developed visual field impairment and a right-sided hemiparesis. Brain MRI revealed bilateral posterior and left parietal ischaemic strokes. Cerebral catheter angiography showed segmental arterial vasoconstriction. A vasodilative therapy with calcium channel inhibitors was started and serial transcranial Doppler ultrasonography demonstrated resolution of cerebral arterial vasoconstriction. The present case illustrates that calcium channel inhibitors may be an effective therapy for segmental cerebral arterial vasoconstriction. However, more clinical data are needed to prove this observation. □ *Reversible segmental cerebral arterial vasoconstriction, Call–Fleming syndrome, calcium channel inhibitor, stroke, treatment*

Priv. Doz. Dr Helge Topka, Department of Neurology, Academic Hospital Bogenhausen, Technical University of Munich, Engschalkingerstraße 77, D-81925 Munich, Germany. Tel. 0049-89-9270-2081, fax 0049-89-9270-2684, e-mail topka@extern.lrz-muenchen.de
Received 13 August 2002, accepted 16 September 2002

Introduction

The Call–Fleming syndrome is characterized by a sudden onset of thunderclap-like headache, focal neurological deficits and seizures, most commonly in women aged 20–50 years (1). The onset of symptoms may be spontaneous, but a clinical association with pregnancy (postpartum angiopathy) (2), migraine (migraine angiitis) (3) and the intake of vasoactive drugs has been described (4–9). The pathophysiological correlate is a reversible segmen-

tal vasoconstriction of cerebral arteries that is frequently associated with focal cerebral ischaemia (1, 3, 4). The phenomenon of reversible cerebral vasoconstriction was described in a variety of conditions, but is still poorly understood (5–9). An association between the syndrome and exposure to vasoactive drugs was noticed (4). We recently evaluated a patient who developed reversible cerebral arterial vasoconstriction (i.e. the Call–Fleming syndrome). The cause of cerebral vasoconstriction remained unknown. In our patient, the calcium channel antag-

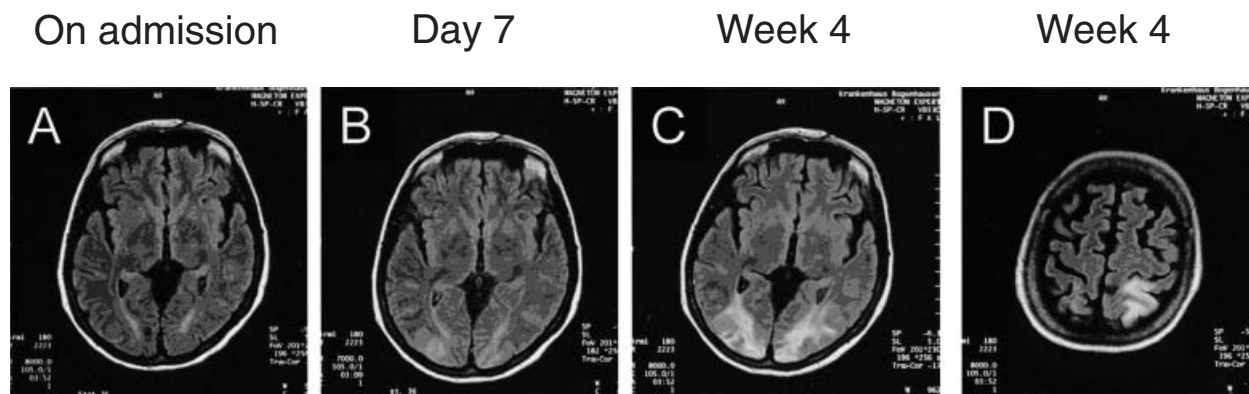


Figure 1 Brain magnetic resonance imaging (MRI) findings. (A) On admission fluid attenuated inversion recovery (FLAIR) MRI showed no abnormalities. (B) On day 7 following admission FLAIR MRI revealed discrete bilateral occipital ischaemic strokes and a left parietal postcentral ischaemic stroke (not shown). (C,D) Four weeks following admission, FLAIR MRI of the brain revealed more clearly the bilateral occipital (C) and left parietal strokes (D) without additional ischaemic areas.

onist nimodipine proved to be sufficient to reverse the cerebral arterial vasoconstriction as assessed by serial transcranial ultrasonography.

Case report

A 63-year-old female developed sudden 'worst ever' headache with nausea. Her past medical history included hypertension, depression and traumatic loss of her right eye 15 years ago. Her medications were metoprolol 50 mg once daily (started 2 years previously), clobazam (periodically 0.5 mg once daily, started 3 months previously) and fluspirilen (1.5 mg i.m. administered once 3 months previously). She denied the intake of any additional medications. She was admitted to an outside hospital, where routine laboratory blood tests, CSF examination and head computed tomography (CT) were unremarkable. She was put on oral analgesia with paracetamol and ibuprofen and was discharged with mild improvement of headache 2 days following admission.

Two days following discharge, she developed 'unbearable' headache and was admitted to our hospital. On admission, her neurological examination was unremarkable. Head CT and brain magnetic resonance imaging (MRI) (Fig. 1A) were normal. CSF examination revealed no cells, a CSF protein level of 43 mg/dl (normal limits 15–45 mg/dl), CSF lactate 1.5 mmol/l (normal limits ≤ 2 mmol/l) and a CSF glucose level of 57 mg/dl (normal limits 45–75 mg/dl), serum glucose level 123 mg/dl). The oligoclonal bands in CSF were negative. Acute headaches recurred frequently and 7 days after admission (11 days after the onset of the headache) she reported

sudden worsening of headache and acute visual blurring. Neurological examination revealed impaired vision of her remaining left eye and a mild right-sided brachio-facial hemiparesis. Systemic blood pressure was within normal limits. Brain MRI with diffusion-weighted imaging at this point showed post-ischaemic lesions within the left parieto-occipital and bilateral occipital regions (Fig. 1B). Transcranial Doppler ultrasonography (TCD) revealed elevated flow profiles of the intracranial vessels with a peak flow in the basilar artery (approx. 150 cm/s; see Table 1). Catheter angiography showed severe, diffuse segmental intracranial vasoconstriction (Fig. 2). CSF analysis was unremarkable. Extensive tests including cardiac ultrasound, complete blood count, lipid profile, prothrombin time, partial thromboplastin time, levels of protein C, protein S, anti-thrombin III, anti-phospholipid antibodies, complement, anti-neutrophil cytoplasmic antibody, antinuclear antibody and anti-double-stranded deoxyribonucleic acid antibody for stroke aetiology were unremarkable. Monitoring of the patient's blood pressure did not reveal values above 150/100 mmHg.

Severe headaches persisted and she was set on oral steroids (1.5 mg methylprednisolone per kg body weight approx. 80 mg, t.i.d.) and oral nimodipine (100 mg t.i.d.). Eight days following admission, the headaches worsened and serial TCD revealed cerebral vasospasm of both middle cerebral arteries and the basilar artery (Table 1). An i.v. therapy with nimodipine (2 mg/h i.v.) and magnesium (1 g 20% magnesium per hour i.v.) was started. A few hours after the onset of i.v. nimodipine and magnesium administration the headaches improved. One day

Table 1 Transcranial Doppler ultrasonography (TCD) machine-derived maximum mean and peak flow values in cm/s measured in the territories of both middle cerebral arteries (MCA) and the basilar artery (BA) during serial TCD examinations

Days from admission	Right MCA		Left MCA		BA	
	Peak	Mean	Peak	Mean	Peak	Mean
7*	81	62	109	83	151	104
8†	162	119	169	126	207	150
9‡	91	63	81	54	75	50
10	–	–	–	–	95	69
11	–	–	94	91	93	82
12§	195	128	145	83	62	42
13	147	102	171	119	129	94
14	126	89	132	96	143	104
15	128	90	126	88	124	82
16	133	93	126	91	124	89
17	133	93	131	95	110	83
18	121	85	119	83	121	88
19	112	78	108	75	108	75
20	59	38	71	40	56	36
21	76	57	71	47	64	42
22	91	58	83	56	72	47
23	112	75	121	85	105	74
24	81	52	71	45	57	38
27	82	52	69	44	52	29
32	104	67	108	71	99	67

Mean and peak flow values were measured at approximately constant depths at different time points within the clinical course.

*Acute worsening of headaches, impaired vision and right sided hemiparesis; a brain MRI (Fig. 1B) and a cerebral catheter angiography (Fig. 2) were performed.

†Acute worsening of headaches.

‡One day following the onset of intravenous nimodipin and magnesium administration.

§One day after the stop of intravenous nimodipine infusion and initiation of oral nifedipine therapy due to an increase of liver parameters.

following the onset of intravenous nimodipine and magnesium administration, TCD documented normal peak flow values of the intracranial arteries (Table 1). On the third day of i.v. nimodipine administration the i.v. nimodipin infusion had to be stopped due to an increase of liver enzymes and an oral administration of nifedipine (20 mg t.i.d.) was started. On the following day, TCD showed cerebral arterial vasoconstriction with increased peak flow values (Table 1). However, serial TCD documented a return to normal peak flow values within 6 days of oral nifedipin therapy (Table 1). At day 17 following admission, MRI angiography demonstrated complete resolution of the cerebral vasoconstriction.

The right-sided hemiparesis resolved completely during the following 2 weeks. Brain MRI 4 weeks following admission revealed no additional ischaemic cerebral infarct areas (Fig. 1C,D) and additional MRI angiography showed no cerebral vasoconstriction. The patient was free of headaches at that time. Perimeter testing revealed a skotoma of

the left central visual field. The remainder of the neurological examination was unremarkable. At this point, the patient was transferred to another hospital for further rehabilitation treatment.

Discussion

This patient developed sudden, 'worst-ever' (thunderclap) headaches, focal neurological symptoms, and reversible cerebral arterial vasoconstriction. The clinical presentation and imaging features are typical of the Call–Fleming syndrome (1, 3, 4). Patients presenting with this syndrome are sometimes misdiagnosed with primary inflammatory cerebral vasculitis. We observed no evidence of inflammation and the immunopathological laboratory findings were unremarkable in our case. In particular, the CSF protein level is commonly elevated in cerebral vasculitis, but was found to be normal in our patient.

Reversible cerebral arterial vasoconstriction has been associated with pregnancy (2), migraine (5),

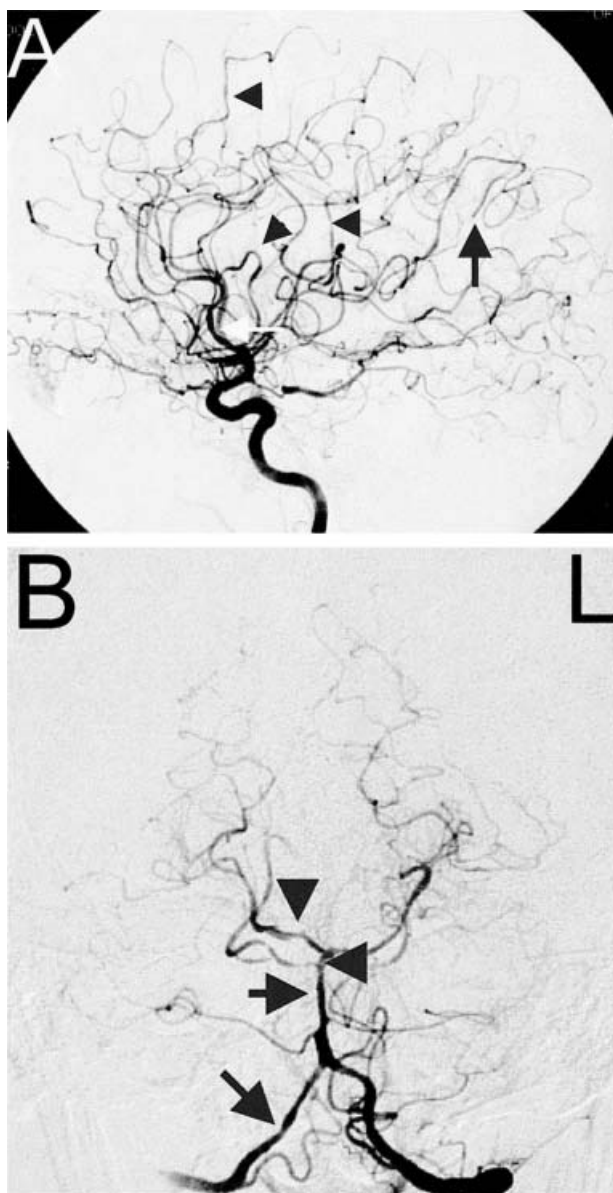


Figure 2 Cerebral catheter angiography. (A) Lateral projection of the right internal carotid artery territory demonstrates several vasoconstrictions of both anterior and the right middle cerebral arteries. Smooth narrowings of the A2 segment of the anterior cerebral artery (white arrow) and of several branches of the middle cerebral artery (arrowheads) are shown. In addition, an occlusion of a parietal branch of the middle cerebral artery is demonstrated (grey arrow). (B) Frontal projection of the left vertebral artery injection shows smooth segmental narrowing of the right vertebral artery between the descent of the posterior inferior cerebellar artery and the basilar artery (arrow). In addition, the proximal basilar artery shows a smooth segmental narrowing after the descent of the anterior inferior cerebellar artery (arrow). Vasoconstrictions are also seen in the right superior cerebellar artery and right posterior cerebral artery (arrowheads).

porphyria (9), and the use of vasoactive drugs (4, 6–8). However, similar to our case, the onset of characteristic sudden severe headache with focal neurological deficits may also occur spontaneously (3, 9–11). No single cause for the manifestation of reversible cerebral vasoconstriction could be identified in our patient. In particular, previous medical history revealed no exposure to vasoactive drugs. She regularly took metoprolol against high blood pressure and rarely clobazam (a benzodiazepin derivative) against recurrent episodes of anxiety. Three months prior to the first occurrence of thunderclap-like headaches, she received 1.5 mg fluspirilen administered once by i.m. injection.

The butyrophenon fluspirilen is a potential neuroleptic drug and blocks dopamine, histamine and α -adrenergic receptors. In the striatum, the blockage of D_2 -receptors results in an imbalance between excitatory cholinergic and inhibitory dopaminergic neurones. This imbalance may cause extrapyramidal movement disorders. Within the mesolimbic system, the blockage of CNS D_2 -receptors causes a decrease of emotional excitability and impulsions. In addition, fluspirilen is an inhibitor of α -adrenergic, serotonergic and histamine receptors within the ascending reticular activating system of the CNS, and blockage of this system results in reduced vigilance. Fluspirilen has no known vasoactive effects and an association between its administration and the manifestation of reversible cerebral vasoconstriction 3 months later is highly unlikely.

In the present case, one striking feature was a rather long interval between the explosive onset of headache and the development of focal neurological deficits. Despite severe headache, brain MRI on admission was normal. One week following admission (11 days following the index headache) focal neurological deficits appeared and brain MRI revealed cerebral infarctions. A latency of several days between the onset of headache and the manifestation of neurological signs and symptoms has been reported (10, 11). Cerebral catheter angiography demonstrated the typical segmental smooth narrowing of cerebral arteries (11).

The most important observation in the present case history was the prompt and effective resolution of cerebral vasoconstriction following the initiation of i.v. nimodipine (and magnesium) administration. Nimodipine is a calcium channel antagonist and causes dilatation of the smooth muscles of arterial blood vessel walls. Magnesium inhibits several intracellular enzyme cycles and causes dilatation of arterial vessel walls. The resolution of cerebral vasospasm could be documented by serial TCD

examinations. After the i.v. administration of nimodipine was stopped due to an increase of liver parameters, signs of vasoconstriction returned as assessed by TCD (see Table 1). Vasodilatative therapy was continued by oral administration of the calcium channel antagonist nifedipin and successive resolution of cerebral vasospasm occurred within 6 days of therapy.

Sturm and Macdonell reported a case of recurrent thunderclap headache associated with angiographically documented cerebral arterial vasoconstriction (10). The patient was treated with i.v. nimodipine, and MR angiography demonstrated improvement in vessel calibre during the treatment. Together with our findings these data suggest that calcium channel antagonists may be important therapeutic agents in the treatment of reversible cerebral vasoconstriction. However, our patient also received oral steroids and i.v. magnesium, which may have contributed to the resolution of segmental cerebral vasospasm. On the other hand, previous case reports failed to show efficiency of calcium channel inhibitors and/or steroids in this condition (2). Therefore further case observations are necessary until therapeutic recommendations for segmental cerebral vasoconstriction can be given.

Today, the pathophysiological phenomenon of reversible vasoconstriction of cerebral arteries is still poorly understood. A variety of aetiologies, such as intake of vasoactive drugs (4, 6–8), metabolic disorders (3, 9), migraine (3, 5) and pregnancy (2) have been discussed. However, the syndrome may also occur spontaneously as in the present case (3, 10, 11). Patients developing sudden-onset headaches should first be evaluated for common conditions, such as subarachnoid haemorrhage and sinus venous thrombosis. Once these are ruled out, non-invasive (TCD, MRI and CT angiography) imaging investigation for cerebral vasoconstriction should be considered. If cerebral arterial vasoconstriction is present, causative conditions, such as subarachnoid haemorrhage, metabolic disorders, and exposure to

vasoactive drugs should be excluded. Treatment options for segmental cerebral arterial vasoconstriction include the therapy of underlying pathologies, discontinuation of vasoactive drugs and, as observed in our case, administration of calcium channel inhibitors may be helpful.

References

- 1 Call GK, Fleming ML, Sealton S, Levine H, Kistler JP, Fisher CM. Reversible cerebral segmental vasoconstriction. *Stroke* 1988; 19:1159–70.
- 2 Lee KY, Sohn YH, Kim SH, Sunwoo IN. Basilar artery vasospasm in postpartum cerebral angiopathy. *Neurology* 2000; 54:2003–5.
- 3 Singhal AB, Koroshetz W, Caplan LR. Cerebral vasoconstriction syndromes. In: Bogousslavsky J, Caplan LR, editors. *Uncommon causes of stroke*. Cambridge: Cambridge University Press, 2001:114–23.
- 4 Singhal AB, Caviness VS, Begleiter AF, Mark EJ, Rordorf G, Koroshetz WJ. Cerebral vasoconstriction and stroke after use of serotonergic drugs. *Neurology* 2002; 58:130–3.
- 5 Molaie M. Serotonin syndrome presenting with migraine-like stroke. *Headache* 1997; 37:519–21.
- 6 Meschia JF, Malkoff MD, Biller J. Reversible segmental cerebral arterial vasospasm and cerebral infarction: possible association with excessive use of sumatriptan and Midrin. *Arch Neurol* 1998; 55:712–4.
- 7 Conde Lopez VJM, Ballesteros Alcalde MC, Blanco Garrate JA, Marco Llorente J. Cerebral infarction in an adolescent girl following an overdose of paroxetine and caffeine combined with theodrenaline. *Actas Luso Esp Neurol Psiquiatr Cienc Afines* 1998; 26:333–8.
- 8 Reneman L, Habraken JB, Majoie CB, Booi J, den Heeten GJ. MDMA ('Ecstasy') and its association with cerebrovascular accidents: preliminary findings. *Am J Neuroradiol* 2000; 21:1001–7.
- 9 Black KS, Mirsky P, Kalina P, Woldenberg Greenberg R, Drehobl KE, Sapan M, Meikle E. Angiographic demonstration of reversible cerebral vasospasm in porphyric encephalopathy. *Am J Neuroradiol* 1995; 16:1650–2.
- 10 Sturm JW, Macdonell RA. Recurrent thunderclap headache associated with reversible intracerebral vasospasm causing stroke. *Cephalalgia* 2000; 20:132–5.
- 11 Slivka A, Philbrook B. Clinical and angiographic features of thunderclap headache. *Headache* 1995; 35:1–6.