

### BRIEF REPORT

# Thrombolytic treatment of ischaemic stroke occurring during a migrainous attack: a case report

#### D Školoudík<sup>1</sup>, M Král<sup>1</sup>, D Šaňák<sup>1</sup>, I Vlachová<sup>1</sup>, P Hluštík<sup>1</sup>, K Michálková<sup>2</sup>, R Herzig<sup>1</sup> & P Kaňovský<sup>1</sup>

<sup>1</sup>Stroke Centre, Departments of Neurology and <sup>2</sup>Radiology, Faculty of Medicine and Dentistry, Palacký University and University Hospital Olomouc, Czech Republic

## Cephalalgia

Školoudík D, Král M, Šaňák D, Vlachová I, Hluštík P, Michálková K, Herzig R & Kaňovský P. Thrombolytic treatment of ischaemic stroke occurring during a migrainous attack: a case report. Cephalalgia 2009. London. ISSN 0333-1024

Authors report a case of young female suffering from the acute ischaemic stroke with right-sided hemiplegia, hemianopsia and hemihypoaesthesia during a migrainous attack without aura. Magnetic resonance imaging detected infarction in the left occipital lobe and occlusion of branches of the posterior cerebral artery (PCA). Combined treatment with systemic thrombolysis and sonothrombolysis was used, leading to the early PCA recanalization, and to a favourable clinical outcome after 1 month. Intravenous thrombolytic treatment administered within the therapeutic window may be useful in cerebral ischaemia associated with migraine when an arterial occlusion is documented.  $\Box$ *Migraine, stroke, ischaemic infarction, thrombolysis, transcranial sonography* 

David Školoudík, Department of Neurology, University Hospital Olomouc, I. P. Pavlova 6, CZ-775 20 Olomouc, Czech Republic. E-mail skoloudik@hotmail.com Received 22 November 2008, accepted 8 March 2009

#### Introduction

The relationship between migraine and ischaemic stroke is very complex. At least four issues should be addressed: (i) migraine as a cause of ischaemic infarction (migrainous infarction); (ii) ischaemic stroke occurring during the attack of migraine (ISODAM), in which migraine could be a requisite coexisting factor, but not the only factor; (iii) migraine attacks triggered by cerebral ischaemia; and (iv) migraine as a risk factor for ischaemic stroke (1, 2).

When stroke occurs during a migrainous attack, prompt detection of aetiopathogenic factors is necessary. Specifically, differentiation between vasospasm in migrainous infarction and thromboembolic brain artery occlusion in ISODAM is crucial for choosing the optimal therapeutic method.

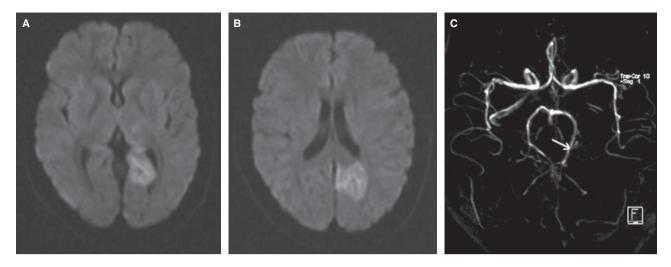
#### **Case report**

A 21-year-old woman had a gynaecological history of menses with regular cycles since 12 years of age,

two elective abortions, and hormonal contraception since 18 years of age. She was an active smoker (50 cigarettes a day) and a social drinker. Her 43-yearold mother and maternal grandmother had suffered from headaches related to menstruation.

Since 16 years of age, the patient had had tension-type headaches localized to the retro-orbital and frontal regions bilaterally, usually occurring in the evening before bed time with no apparent trigger. The headaches typically lasted for 2–4 h and a good response to non-steroidal analgesics (acetylsalicylic acid and paracetamol) was observed. One week before admission to the hospital, for the first time in her life, six typical attacks of migraine without aura accompanied by photophobia and phonophobia occurred. She had never used triptans or ergomine. She fulfilled the criteria for migraine without aura, as defined by the International Classification of Headache Disorders, 2nd edn criteria.

On the day of admission, upon awakening, the patient developed a headache localized to the left frontal and temporal regions, accompanied by



**Figure 1** (A–C) Magnetic resonance: MR imaging diffusion-weighted axial sequences demonstrate areas of high signal indicating acute cerebral infarction involving the left occipital lobe (A, B) and MR angiography demonstrates occlusion (arrow) of left posterior cerebral artery branches (C).

photophobia, phonophobia and nausea, followed 1 h after the headache onset by right-sided central hemiparesis (progressing to hemiplegia), hemihypoaesthesia, hemianopsia and vomiting. These symptoms [11 points on the National Institute of Health Stroke Scale (NIHSS)] lasted for 100 min at the time of admission.

Brain magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) performed 116 min after stroke onset revealed acute infarction in the territory of the left posterior cerebral artery (PCA) and occlusion of the left PCA branch (Fig. 1).

Duplex sonography of the cervical arteries performed 145 min after stroke onset showed normal findings in the cervical vessels. However, occlusion of the occipital branches of the left PCA with decreased resistance indices in the middle cerebral arteries (MCA) were detected by transcranial colour-coded sonography (TCCS). Laboratory findings (basic biochemistries, haemocoagulation and blood count) were normal.

The patient was a candidate for intravenous thrombolysis (IVT) (recombinant tissue plasminogen activator, 0.9 mg/kg, 47 mg total) in combination with transcranial Doppler (TCD) monitoring (sono-thrombolysis). Administration started 150 min after the stroke onset. A TCCS examination 30 min after the therapy was initiated showed partial recanalization of the left PCA branches with complete recanalization after 12 h. Clinical improvement by 2 points on the NIHSS was detected 2 h later. Mild right-sided central hemiparesis, hemihypoaesthesia and hemianopsia persisted after 24 h (4 points on the NIHSS). A control MRI including intracranial MRA, performed after 10 h, showed subacute infarctions in the left PCA territory and in the left thalamus, a fuzzy-border hyperintense area in the left temporal lobe and complete recanalization of the left PCA. Aspirin administration as a secondary stroke prevention was started 24 h after thrombolysis. Lowdose enoxaparine was used during the first week to prevent deep venous thrombosis.

Migrainous attacks without aura appeared every 2 days during the next week and on day 5 resolved after unrepeated application of sumatriptan 50 mg (Rosemig®). A TCCS examination performed during another attack of migraine on day 7 showed peripheral vasospasms in the territories of the right MCA and both PCAs (Fig. 2). After failure of calcium channel blockers (both in the reduction of headache frequency and in the vasospasms reversion), prophylactic therapy with topiramate was started and a reduction of the frequency of migraine was observed during the next 2 weeks. Subsequently, only tension headache with good effect of oral non-steroidal analgesics occurred.

Twenty-four-hour Holter electrocardiogram monitoring, x-ray of the heart and lungs, and transthoracic and transoesophageal echocardiography showed normal findings. On haemocoagulation assessment, only a borderline decrease in factor VII (73%) was detected, all other findings (antitrombin III, methylenetetrahydrofolate reductase mutation, antiphospholipid antibodies, factors II and VIII, C protein, activated protein C resistance, free S protein, apc1 and apc2) were normal.

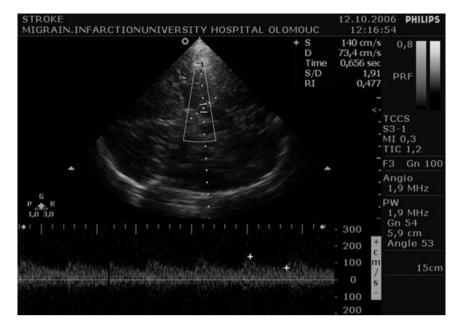


Figure 2 Transcranial colour-coded sonography demonstrates turbulent accelerated flow in vasospasm of the left posterior cerebral artery.

Incomplete right-sided homonymous hemianopsia was the only pathological finding present at discharge on day 10 (NIHSS, 2 points), with further improvement to only partial hemianopsia (NIHSS, 1 point; modified Rankin score, 2 points) present on day 30.

#### Discussion

Systemic thrombolysis is an effective therapy for acute ischaemic stroke (3). However, this therapy may be questionable in patients with migrainous infarction or ISODAM because vasospasms could play a more important role in the infarction pathogenesis than thromboembolism as a common cause of the majority of ischaemic strokes (1, 2, 4, 5). ISODAM is a very rare cause of stroke, first described by Milhaud et al. (5). In contrast to migrainous infarction, vasospasms are not the only pathogenic factor in ISODAM, where a role of thromboembolism is hypothesized (1, 2, 5).

Although vasospasms are likely to play an important role as well, PCA occlusion was the direct cause of infarction in the patient reported here. Moreover, it is questionable if hemiplegia was caused by infarction in the PCA cerebral territory or by an additional occlusion in the MCA branches not detected by MRA or TCCS.

Factors that may contribute to stroke in migraine include changes during cortical spreading depression with hyper- or hypoperfusion of neural tissue, vasospasm and endothelial dysfunction (6). The first TCCS examination detected vasodilation in both MCA territories. This finding is typical of a migrainous attack, but is less frequent in the interictal phase (7). A control TCCS examination, performed during one of the subsequent attacks of migraine, detected vasospasms in intracranial arteries (MCA and PCA), which were maximum in the symptomatic left PCA. One can hypothesize that a severe vasospasm, which may be caused also by serotonin release (8, 9), in the left PCA during the migrainous attack caused a significant decrease of the flow with turbulence in the distal part of the arterial territory with subsequent stagnation of blood flow and arterial thrombosis. Furthermore, cerebral circulation may be influenced also by oestrogen (6).

Hormonal contraception and cigarette smoking represent also prothrombotic risk factors in the presented case (10–14). Release of serotonin may also influence thrombus formation, although its role is still controversial (15–19). All other causes of ischaemia often occurring in patients with migraine, such as patent foramen ovale, lupus anticoagulant, cervical carotid dissection, arteriovenous malformation and hyperactivity of the clotting system (6, 20, 21), were excluded in the presented case.

Neuroimaging has demonstrated the posterior circulation as being most vulnerable in migraineurs, although the reason for this distribution is unclear (6). As the vasospasms in migraineurs are diffuse (7), a simultaneous vasospasm in the MCA territory could lead to a restriction of collateral flow to the PCA territory and to the marked clinical manifestation of symptoms of ischaemia in the presented case.

Acute PCA occlusion was detected using both MRA and TCCS. Furthermore, recanalization was diagnosed during TCCS monitoring of IVT. Partial PCA branch recanalization was detected 30 min after the start of therapy. This early recanalization was followed by marked improvement of neurological deficits (7 points on the NIHSS during the first 24 h). TCD monitoring was not only shown to be an appropriate method for the monitoring of intracranial artery recanalization, but probably also accelerated the recanalization (so-called sono-thrombolysis), as demonstrated by recent studies (22).

Reperfusion therapy represents the most efficient treatment of acute stroke caused by arterial occlusion. At present, pharmacological and mechanical recanalization methods can be used (23). IVT, performed within a 3-h window, is the only fully established reperfusion method for acute ischaemic stroke (3). The use of IVT is not contraindicated, even in patients with migrainous infarction or ISODAM, where an important role of vasospasm is suspected (3). However, the IVT effect could be controversial in cases without detected arterial occlusion. In these cases, the role of diagnostic methods, such as MRA, computed tomographic angiography, TCCS or digital subtraction angiography, becomes crucial.

Observational studies have shown that the natural clinical outcome in patients with migrainous infarction or ISODAM could be more favourable than in patients with a thromboembolic origin of stroke. Milhaud et al. (5) reported a favourable outcome in 72% of migraineurs, compared with 63% of patients in the control group, influenced especially by lower age and a lower number of comorbidities in migraineurs. Detailed analyses of stroke studies demonstrated a dependency of favourable clinical outcome primarily on initial NIHSS, patient age, localization of the arterial occlusion, time to recanalization and comorbidities. The use of reperfusion therapy and its complications (brain oedema and spontaneous intracerebral haemorrhage) are other important factors influencing the outcome (23, 24). These factors also play a similar role in patients with stroke during a migrainous attack.

In most cases, the diagnosis of migrainous cerebral infarction or ISODAM is made by the exclusion of other causes of cerebral ischaemia, for which the results of a large battery of diagnostic tests are required. Thus, this diagnosis is usually established outside the IVT therapeutic window. Also in the reported case, the final diagnosis was confirmed after this window. Nevertheless, the use of recanalization therapy within a therapeutic window is reasonable in the case of cerebral infarction and the presence of cerebral arterial occlusion of any aetiology.

The patient did not fulfil the diagnostic criteria of migrainous infarction (25), because of the absence of aura (also in the history), although the other risk factors in the presented case were compatible with this diagnosis-female gender, age <45 years, the use of oral contraceptives, smoking and infarction localization in the PCA territory (26). Also, arterial dissection was excluded using MRA and neurosonological examination. Vasospasms documented in the presented case may occur also in thunderclap headache attributed to reversible cerebral vasoconstriction syndrome and may be associated with similar clinical symptoms (explosive headache, nausea, photophobia). This syndrome is also more frequent in women and may be complicated by ischaemic stroke (27). However, the presence of thromboembolic arterial occlusion was found in the presented case. Based upon the above-mentioned findings, the ISODAM diagnosis was established.

The use of triptans is contraindicated in patients with a history of ischaemic vascular event, including ischaemic stroke or transient ischaemic attack. However, according to the results of more recent studies, the use of triptans is not associated with increased risk of any ischaemic events, including stroke and myocardial infarction, ischaemic heart disease, cardiovascular death and mortality (28, 29). Sumatriptan also had no significant effects on the blood pressure limits of cerebral blood flow autoregulation in the experimental study (30). Triptan therapy was used only once in the presented case in the treatment of a prolonged migrainous attack non-responding to analgesics, calcium channel blockers and magnesium. This off-label use of triptan was performed due to the failure of the mentioned therapy with patient's consent.

#### Conclusion

The successful treatment of stroke of unknown aetiology occurring during a migrainous attack in a young female is reported. If thrombotic occlusion of an intracranial artery is detected, IVT, in possible combination with another recanalization method, should be used to achieve early arterial recanalization so as to increase the chance of a favourable clinical outcome.

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