

# One person – Four different types of headache: Coincidence or a common pathophysiological link?

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## Abstract

There is increasing evidence about a link between migraine, cerebral artery dissection and reversible cerebral vasoconstriction syndrome. We present a case of a patient who had all three diagnoses. The clinical evaluation of this patient was further complicated by a post-dural puncture headache, which added to the three types of headache already known to the patient. This clinical case supports the association between migraine, cerebral artery dissection and reversible cerebral vasoconstriction syndrome and highlights the importance of a precise history taking in establishing the correct diagnosis in patients with headache.

## Keywords

Migraine, reversible cerebral vasoconstriction syndrome, cervical artery dissection, post-dural puncture headache

A 43-year-old female patient presented to our emergency department. Two months prior to admission, she realized bioccipital headache of minor intensity (2/10 on the visual analogue scale (VAS)). Two weeks prior to admission, the headache worsened in severity (10/10 on the VAS) with superimposed thunderclap-like headache attacks lasting for 5–10 min. The attacks were associated with dizziness, paraesthesia in the right arm and scintillating scotoma in both eyes. In her past, the patient had a *history of migraine without aura* with rare attacks of one-sided headache with nausea, vomiting, photophobia and phonophobia. The last two migraine attacks occurred 1 and 5 years prior to admission. Within the last year, her body weight increased by 6 kg (82–88 kg) without a specific explanation. The clinical examination showed an obese female patient with a body mass index of 30 kg/m<sup>2</sup> with normal vital signs. A thorough clinical examination was normal. The magnetic resonance imaging (MRI) of the brain showed irregularities of the middle cerebral artery (MCA) on both sides in the M1 segment without evidence of ischaemia in diffusion-weighted images, intracerebral haemorrhage, dissection of cerebral artery or sinus venous thrombosis. The cerebrospinal fluid (CSF) was normal with an opening pressure of 17 cm CSF. The follow-up MRI of the brain on the next

day showed an improvement of the MCA irregularities. Transcranial duplex sonography demonstrated an increase of blood flow velocities in both M1 segments of the MCA (M1 left: 176/82 cm/s, M1 right: 152/58 cm/s, corresponding to 50% stenoses). Screening tests for vasculitis and phospholipid antibodies and use of illicit drugs were negative (ANA, ANCA, anti-cardiolipin antibodies). The diagnosis of a *reversible cerebral vasoconstriction syndrome* (RCVS) was made and treatment with nimodipine and magnesium was initiated. The headache improved, and the patient was discharged home.

Three months later, the same patient presented to our emergency department with a third type of headache. This headache was strictly on the right side of the back of the head and neck with some radiation over the right side of the head. It was first noticed 2 weeks prior to the second admission. Initially, it was barely noticeable and then slowly

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progressed to a final intensity of 8–9/10 on the VAS. The character was pulling, pulsating, and worsened with recumbency, physical exertion, pressing (Valsalva manoeuvre) and with head movements to the left and forward. Headaches were associated with phonophobia, nausea and scintillating scotoma on the entire visual field. Headaches differed from the headaches of the first episode and from the usual migraine attacks by the continuous duration and mechanical triggers. No head or neck trauma was reported. The neurological examination in the emergency room was normal, but a further increase in the body weight of 3 kg (from 88 kg to 91 kg, BMI 31.05 kg/m<sup>2</sup>) was observed. A CSF examination performed with a traumatic needle (the attempt to perform the lumbar puncture with an atraumatic needle was unsuccessful) was normal with an opening pressure of 20.5 cm CSF. ANA, ANCA and test regarding the use of illicit drugs were again negative. An MRI of the brain showed neither irregularities of the MCA nor ischaemia or haemorrhages. However, there was a *dissection of the right vertebral artery (VA)* in V2–V3 segment, which had not been present in the MRI done for the first headache. After the lumbar puncture, the patient developed *post-punctional headaches*, which declined in strict recumbent position.

## Discussion

We present a patient who experienced four different types of headaches: she had a history of migraine without aura (ICHD III Code 1.1.), developed an RCVS (ICHD III Code 6.7.3.1.), followed by a VA dissection (ICHD III Code 6.5.1.1.) and post-dural puncture headache (ICHD III Code 7.2.1.). While it is obvious that the post-punctional headache was a complication of the lumbar puncture, the main question arises whether the other three types of headache in one single patient are pure coincidence or whether there is a potential link. From a clinical perspective, it is not uncommon that patients with a history of migraine develop secondary headaches of migrainous phenotype, as did our patient during the VA dissection.<sup>3</sup> It is therefore important to emphasize that, in migraineurs, alterations of headache phenotype, especially in the direction of ‘red flags’, such as continuous headache or headache worsening by head movement, should always result in further investigation.<sup>1,2</sup> From a pathophysiological point, migraine, RCVS and cervical artery dissection (CAD) are three distinct headache syndromes (ICHD-III) that might share more than just this main clinical symptom of headache.<sup>3</sup> Mawet et al. performed a systematic review on this topic and found common and complex epidemiological, clinical and genetic features, which might explain their association.<sup>3</sup> Our individual clinical case unifies all three headaches with an additional fourth (post-dural puncture headache) and supports this hypothesis clinically.

## Migraine and CAD

A large international case–control study on more than 1600 patients and a meta-analysis gathering five case–control studies investigated the association between migraine and CAD. Being a migraineur increased the risk of suffering a CAD by OR 2.01, 95% CI 1.33–3.19.<sup>4,5</sup> The mechanism of this increased risk is unknown. Apart from genetic variants, other hypotheses involve a dysfunctional transforming growth factor beta (TGF- $\beta$ ) pathway, involvement of matrix metalloproteinases and the methylenetetrahydrofolate reductase metabolism.<sup>3</sup>

## CAD and RCVS

The association between CAD and RCVS has been postulated in multiple case reports and has been confirmed in a prospective cohort study of 20 patients with both conditions, representing 12% of consecutive RCVS patients and 7% of consecutive CAD patients.<sup>3,6,7</sup> The clinical presentation of RCVS plus CAD did not differ from that of isolated RCVS. However, in addition to the usual clinical presentation, associated neck pain was present in 75% of cases.<sup>6</sup> The underlying mechanisms remain unclear. Further, the sequence of pathologies is unknown, that is, whether RCVS induces CAD, or vice versa.<sup>6</sup> In our patient, RCVS has been identified prior to the VA dissection. Eventually a shared genetic predisposition for RCVS and CAD, potentially linked to migraine, is possible that remains to be confirmed, for example, in genetic studies.<sup>6</sup>

## Migraine and RCVS

It is unknown whether being a migraineur is a risk factor for an RCVS.<sup>3</sup> There is some overlap in respect of epidemiology (both are more common in female) and pharmacology (some anti-migraine medication might trigger RCVS), but the prevalence of migraine appears similar in the general population (12–15%) and in RCVS.<sup>8,9</sup> Further controlled studies would be necessary to clarify this.<sup>3</sup>

## What could be the potential link between migraine, RCVS and CAD?

The pathophysiological link between all three conditions remains unknown. Hypotheses involve endothelial dysfunction, which has been found in migraineurs and might explain the increased risk of stroke in migraine or impaired vasoreactivity related to endothelial dysfunction in migraineurs with CAD.<sup>3,10,11</sup>

## Conclusion

Our patient underlines the hypothesis of a common mechanism connecting migraine, CAD and RCVS. The mechanism might involve endothelial dysfunction or impaired vasoreactivity. Patients with migraine, who

experience a change in headache phenotype, should be investigated for secondary headaches, especially when red flags for CAD or RCVS are present.<sup>2</sup>

Careful history taking, clinical information and imaging may help to differentiate between the three types of headache. Early diagnosis is important due to the risk of potential dangerous complications (i.e. intracranial artery dissection with potential subarachnoidal haemorrhage, intracerebral haemorrhage, multiple cerebral infarction due to RCVS, reversible brain oedema, etc.) in untreated secondary headaches.

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