

Cerebral venous thrombosis

Cerebral venous thrombosis – headache is enough

H-C Diener

Considering CVT for progressive headache

In this issue the paper by Cumurciuc *et al*¹ (pp 1084–7) reports 17 cases from 123 consecutive patients with cerebral venous thrombosis (CVT) in whom the only neurological sign was headache. The series is biased by the fact that the Department of Neurology of the Lariboisiere Hospital in Paris has particular competence both in headache and stroke, and runs an emergency headache centre where patients can consult a headache specialist without long waiting times. What are the lessons to be learned from this paper?

- (1) Computed tomography (CT) without contrast is not sensitive enough to rule out CVT in patients with progressive headache.
- (2) Most patients with CVT had risk factors for venous thrombosis. The combination of unexplained headaches with risk factors like oral contraceptives,² systemic lupus erythematosus (SLE), or recurrent venous thrombosis justifies the use of CT with contrast or magnetic resonance imaging (MRI).
- (3) The new classification of the International Headache Society still includes the entity of primary thunderclap headache.³ The authors disagreed within themselves whether a primary thunderclap headache

exists. I am convinced that all patients with thunderclap headache have an underlying cerebral disease, which has to be identified. Symptoms include warning leaks of aneurysms, other cerebral bleeds, meningeal inflammation, and, as shown in this paper, cerebral venous thrombosis.

- (4) An unexplained question is whether the prognosis of patients with CVT and headache as the only symptom is similar to patients with focal neurological signs or epileptic seizures. The overall prognosis of CVT is much better than previously suspected.^{4–6} Therefore it would be interesting to know whether these patients should be treated with iv heparin, as was the case in the study from Paris, and how long anticoagulation should be sustained.
- (5) A particular problem is lateral sinus thrombosis. The group led by Bousser is experienced enough to be able to distinguish between sinus thrombosis and sinus dysplasia or aplasia. Less experienced neurologists might mistake sinus dysplasia for thrombosis and patients are exposed unnecessarily to long term anticoagulation.
- (6) Patients in this study were identified as patients with CVT and asked

for symptoms. It would be of interest to perform a prospective study the other way around. The question is how many patients with new and progressive headache or patients with thunderclap headache have CVT. In this way one could perform a cost-benefit analysis of more extended imaging with computed tomography angiography (CTA), magnetic resonance angiography (MRA), magnetic resonance venography (MRV), or traditional angiography.

In summary this important paper has sharpened my view of patients with progressive or thunderclap headache and will prompt me more often than in the past to consider CVT.

J Neurol Neurosurg Psychiatry 2005;**76**:1043.
doi: 10.1136/jnnp.2004.061879

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Whiplash injury

Whiplash injury may deregulate the biological clock

M G Smits

Several risk factors may predispose to circadian rhythm disturbances

In this issue Bloch *et al*¹ (pp 1178–80) describe a patient who developed a free running circadian rhythm after a whiplash injury. The concisely documented case report strongly suggests that a whiplash injury may result in a treatable circadian rhythm disorder. This is important for neurologists and other caregivers involved in patients with a chronic whiplash syndrome (CWS).

The demonstration of a disturbed circadian rhythm (by clinical history, and supported by actigraphy and salivary melatonin) can help CWS patients, people in their environment, and insurance companies to understand one of the possible reasons why sleep, concentration, and memory may be disturbed after a whiplash trauma. A disturbed circadian rhythmicity is a well known cause of these symptoms.²

The possibility of a circadian rhythm disorder following a whiplash injury was demonstrated not until the early nineties of the last century by Patten *et al*.³ They described a 13 year old boy who developed a delayed sleep phase syndrome after a whiplash injury. From that time on several other studies confirmed their findings.⁴

The reason why a whiplash injury can disturb circadian rhythmicity is not well

understood. Nagtegaal *et al*⁵ suggested that a whiplash injury might damage the cervical part of the neural connections between retina and pineal gland. Consequently the endogenous melatonin rhythm delays, resulting in a delayed sleep phase syndrome.

Bloch *et al*¹ found an aneurysm that might have damaged the nucleus supra-chiasmaticus—the location of the biological clock. If this is true, then neurologists should see circadian rhythm disturbances more frequently in patients with aneurysms or tumours in the vicinity of the nucleus supra-chiasmaticus. It seems unlikely that the aneurysm should have deprived the biological clock from all light-dark information, which plays a key role in the development of free running circadian rhythms. The aetiology of the aneurysm is uncertain. The lack of clear clinical symptoms of the aneurysm makes a posttraumatic origin unlikely, so probably the aneurysm pre-existed. In that case the alternative explanation of the authors for the origin of the circadian rhythm disorder is more reliable. Namely the patient could have a predisposition to a short circadian period, which she did not manifest before the accident because of her regular lifestyle. The phase of convalesce at

home could have unmasked the short circadian period.

Several risk factors such as clock gene polymorphisms, and irregular lifestyle may predispose to circadian rhythm disturbances. The presence/absence of some of these risk factors may explain why the same whiplash injury causes circadian rhythm problems in one patient and not in the other.

Non-pharmacological treatment with social “zeitgebers” can improve circadian rhythms, as the case report shows. Well timed bright light, chronotherapy, and melatonin³ are other possibilities to shift circadian rhythms into the desired direction.

It can be expected that more studies will be published in the future showing the importance of biological clock functions in cervical and brain injuries. They will encourage placebo controlled trials comparing the effectiveness of different treatments.

J Neurol Neurosurg Psychiatry 2005;**76**:1044.
doi: 10.1136/jnp.2004.062034

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Risk factor profile

Does the risk factor profile have predictive value for the site of atherosclerosis?

H Sinzinger

Inflammatory markers are significantly higher in patients with carotid atherosclerosis than in those with middle cerebral artery (MCA) infarcts

Atherosclerosis is increasingly linked with inflammation, a claim already made by Rudolf Virchow in 1856. Vascular biology has demonstrated that inflammation also plays a key role in stroke development. The best examined inflammatory marker is C-reactive protein (CRP). High sensitivity (hs)-CRP predicts the risk not reflected by traditional risk factors¹ for stroke and coronary heart disease (CHD). Interleukin-6 is an even better predictor than CRP and correlates with stroke severity, infarct volume, and long term outcome and is an independent predictor of stroke²; hs-CRP is a more valuable predictor than low density lipoprotein cholesterol (LDL). As hs-CRP and LDL are additive predictors, they identify different risk factors.

The CRP gene markedly accelerates atherosclerosis, indicating an active role. CRP is locally generated within the arterial wall. Intraplaque inflammation may attenuate invasion of endothelial progenitor cells and has been postulated to play a crucial role in thinning of the lesion cap and eventual rupture. Ultimate local differences in CRP have not yet been studied.

In this issue, Bang *et al*³ (*see pp 1128–34*) demonstrate that inflammatory markers are significantly higher in patients with carotid atherosclerosis than in those with middle cerebral artery (MCA) infarcts. They observed an inverse correlation between MCA atherosclerosis and CRP after adjusting for age/sex and stroke severity and concluded that MCA lesions may be more stable and require differential therapeutic approaches. MCA atherosclerosis patients may therefore be unlikely to benefit from statins.

However, comparing risk factor prevalence does not exclude all potential pitfalls. Lipids and lipoproteins can be reliably assessed only within 48 h after the acute event.⁴ Inflammatory response varies in the acute phase. As blood was drawn over a range of 1 week, correlation of lipid with non-lipid parameters may be misleading.

In addition, other factors may have influenced the data, such as obesity, known to increase CRP and oxidation injury; in fact, the strongest correlation is with waist circumference. Periodontal disease, chlamydia pneumonia, *Helicobacter pylori* or cytomegalovirus, physical activity, NYHA class, positive family history, nutrition, etc could also be responsible for increased CRP. Was there a difference between the groups examined by Bang *et al*? What was the reason for extreme CRP elevation in three patients?

Normal CRP is zero. As even minor elevation of CRP increases vascular risk, it needs to be treated and all potential causative factors should be examined. However, the prognostic value of elevated CRP, even if estimated at different time intervals,⁵ is definite, although data based on CRP measured during the acute phase are contradictory.⁶

In the western world, life style risk factors could result in elevation of CRP. However, as most people do not make recommended life style changes, what is left? Drugs?

Many questions remain. Is the greatest reduction in stroke risk achieved in patients with higher pre-therapeutic CRP⁷ or is a lower CRP achieved by statins an indicator of better outcome? Different statins may have different effects on inflammatory response. A

greatly varying individual LDL response on statins has been documented, but not yet examined for inflammatory response. What is the role of pleiotropic statin effects in stroke? Should patients with higher CRP receive more potent statins or higher doses known to lower CRP more severely? Should patients with extracranial atherosclerosis despite normal lipid values receive statins for primary prevention? Treating to new targets (for LDL and CRP) enhances the benefit in CHD. Does the same apply for stroke? Is there a difference for intra- and extracranial or large and small vessels or race?

Different risk factor profiles and pathogenetic mechanisms may favour atherogenesis at different vascular sites (as shown for lipoproteins, smoking, and diabetes). To search for different treatments should be a future priority. The claim that MCA atherosclerosis patients are unlikely to benefit from statins is not yet substantiated sufficiently for clinical consequence.

J Neurol Neurosurg Psychiatry 2005;**76**:1045.
doi: 10.1136/jnnp.2005.063297

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