Whiplash injury may deregulate the biological clock

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Several risk factors may predispose to circadian rhythm disturbances

In this issue Bloch et al (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.

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. 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.

The reason why a whiplash injury can disturb circadian rhythmicity is not well understood. Nagtegaal et al 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 found an aneurysm that might have damaged the nucleus suprachiasmaticus—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 suprachiasmaticus. 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 convalescence 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 melatonin 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.

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

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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 factors 1 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 stroke 2. 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 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, lifestyle risk factors could result in elevation of CRP. However, as most people do not make recommended lifestyle changes, what is left? Drugs?

Many questions remain. Is the greatest reduction in stroke risk achieved in patients with higher pre-therapeutic CRP? 7 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 factors and pathogenetic mechanisms may favor 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.


REFERENCES