Subarachnoid haemorrhage

Unravelling the causes of cerebral damage in subarachnoid haemorrhage: might biomarkers help?

A A Rabinstein

The concentration of neurofilament high chain in CSF may represent a biomarker for ischaemic axonal damage

Aneurysmal subarachnoid haemorrhage (SAH) is very often associated with significant functional sequelae. The causes of cerebral injury in this condition are multiple, including the immediate effects of the initial bleeding (vasoparalysis, possible ischaemia, brain oedema, and sudden rise in intracranial pressure), early or delayed hydrocephalus, delayed ischaemia due to vasospasm, systemic complications (such as infections and hyponatraemia), and iatrogenic complications (for example, occlusion of penetrating arterial branches during clipping or coiling of the ruptured aneurysm).¹ In this issue of the journal, Petzold *et al* (see pages 753–9) present their provocative findings suggesting that secondary axonal degeneration may be responsible for poor recovery after SAH.²

The authors serially collected cerebrospinal fluid (CSF) samples from 17 patients with SAH and hydrocephalus requiring external ventricular drainage. Using these samples, they measured the concentration of neurofilament high chain (NfH), a previously validated marker for axonal degeneration. They found that CSF NfH levels had a direct correlation with the clinical severity of SAH at presentation and an inverse correlation with functional outcome at 3 months. On average, CSF NfH concentrations were ninefold greater in patients with unfavourable recovery and peaked 7 days after SAH. Furthermore, an increase in the daily levels of CSF NfH was uniformly seen in patients with poor outcome but was

very unusual among patients with favourable outcome. The authors interpreted these data to indicate that CSF NfH levels denote a process of secondary progressive axonal damage.

As is appropriate for hypothesis-raising research, this study raises more questions than it answers. The findings indicate that axonal damage develops as a consequence of SAH and, not surprisingly, correlates with greater clinical severity of SAH at presentation and poor functional recovery. However, the study does not clarify what causes the axonal injury.

Delayed vasospasm is widely considered to be the most important modifiable cause of secondary cerebral damage. It is more common and severe in patients with worse clinical status at presentation and follows a fairly predictable course, which usually reaches its maximal intensity 7 days after the initial bleeding.³ Unfortunately, the study by Petzold *et al* does not include any information on whether their patients had clinical, ultrasonographic, or radiological evidence of vasospasm. Lack of information on follow-up brain images impedes assessment of the relationship between ischaemic lesions and levels of CSF NfH. Therefore, we cannot discern if the outcome of the patients in this study was related to delayed ischaemic damage from vasospasm. In fact, the maximal levels of CSF NfH were noted at the same time that one would anticipate the maximal effects of vasospasm. Thus, CSF NfH levels may represent a biomarker for ischaemic

axonal damage from vasospasm. This is a particularly interesting hypothesis because the tools currently used to diagnose vasospasm (cerebral angiography, transcranial Doppler) often fail to detect the development of delayed subcortical ischaemic damage.^{4,5}

The distinction between the primary versus secondary injury has practical relevance since our neuroprotective treatments have much greater chances of success when administered prior to the insult. While the increasing levels of neurofilament concentration indicate ongoing axonal damage, they do not prove such damage is delayed. It is possible that the elevation in CSF NfH level may reflect axonal damage triggered by the initial insult but expressed at a later time as the axons degenerate following irreversible injury to the neuronal body by the effects of the primary bleeding.

This study represents a good start and should be followed by more research to validate these findings and delineate their significance. Biomarkers such as CSF NfH may prove valuable for the diagnosis and prognosis of SAH. Moreover, they may hold keys to unravel the complex pathophysiology of brain damage in this condition and to design future therapeutic strategies and monitor their effectiveness.

J Neurol Neurosurg Psychiatry 2006;**77**:711.
doi: 10.1136/jnnp.2006.089581

Correspondence to: Dr Alejandro A Rabinstein, Mayo Clinic College of Medicine, 200 First Street SW, Mayo W8, Rochester, MN 55905, USA; rabinstein.alejandromayo.edu

Competing interests: None declared.

REFERENCES

- 1 van Gijn J, Rinkel GJ. Subarachnoid haemorrhage: diagnosis, causes and management. *Brain* 2001;**124**:249–78.
- 2 Petzold A, Keir G, Kay A, *et al*. Axonal damage and outcome in subarachnoid hemorrhage. *J Neurol Neurosurg Psychiatry* 2006;**77**:753–9.
- 3 Rabinstein AA, Wijdicks EF. Cerebral vasospasm in subarachnoid hemorrhage. *Curr Treat Options Neurol* 2005;**7**:99–107.
- 4 Rabinstein AA, Friedman JA, Weigand SD, *et al*. Predictors of cerebral infarction in aneurysmal subarachnoid hemorrhage. *Stroke* 2004;**35**:1862–6.
- 5 Shimoda M, Takeuchi M, Tominaga J, *et al*. Asymptomatic versus symptomatic infarcts from vasospasm in patients with subarachnoid hemorrhage: serial magnetic resonance imaging. *Neurosurgery* 2001;**49**:1341–8.