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Does disturbed homocysteine and folate metabolism in depression result from enhanced oxidative stress?

In their recent article, Bottiglieri *et al* describe increased homocysteine concomitant with decreased folate concentrations in a subgroup of patients with depression.¹ In addition, some relation between reduced folate availability and disturbed monoamine metabolism was found. The close relation between increased homocysteine and reduced folate concentrations, which was described previously in other clinical conditions such as cardiovascular and cerebrovascular diseases is usually ascribed to a reduced dietary intake of folate, and dietary supplementation with folate is capable of reducing hyperhomocysteinaemia.

The coincidence described of disturbed homocysteine and monoamine metabolism may shed some additional light to the possible mechanism underlying this metabolic abnormality. Both metabolic pathways depend on the presence of reduced pteridine species: (1) the biosynthesis of methionine requires supply of methyl groups from methyl-5,6,7,8-tetrahydrofolic acid, deficiency of which results in hyperhomocysteinaemia; (2) biosynthesis of serotonin, dopamine, and noradrenaline (norepinephrine) depends on the presence of 5,6,7,8-tetrahydrobiopterin, deficiency of which thus results in monoamine deficiency. Both tetrahydropteridines are recycled by dihydropteridine reductases²; both compounds have strong reducing capacities and are thus rapidly oxidised by oxidising chemicals. Interestingly, recent studies show that depression is associated with activation of the immune system,³ and it is even speculated that an infectious agent might be involved. Immune system activation is accompanied by an increased production of reactive species by cytotoxic cells such as activated monocytes and macrophages to achieve antimicrobial and cytotoxic activities. Activated human monocytes/macrophages also release increased amounts of neopterin—another pteridine derivative—which is a sensitive index for the mediation of cell mediated immune reactions in patients.⁴ Recent data also point to a new functional aspect of neopterin—namely, to enhance oxidative processes.⁴ Increased concentrations of neopterin have been described in patients with depression.³ Therefore the question arises whether oxidative stress rather than insufficient dietary intake of folate is the basis of 5,6,7,8-tetrahydrofolate and also 5,6,7,8-tetrahydrobiopterin deficiency. Interestingly, in patients with Alzheimer's dementia a similar relation has already been demonstrated: hyperhomocysteinaemia was associated with reduced folate concentrations, but also an increased degree of immune activation could be detected in the same patients.⁵ There is good reason to think that the scenario might be similar in patients with depression, and enhanced oxidative stress due to chronic immune system activation is a major cause of the loss of reductants such as

5,6,7,8-tetrahydrofolic acid and 5,6,7,8-tetrahydrobiopterin.

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Reynolds and Botiglieri reply:

We thank Widner *et al* for suggesting an explanation of our findings of impaired folate and monoamine metabolism in some patients with depression.

The relation between homocysteine and folate is well established, which is why we included it in our study. We agree that simply dietary deficiency is an inadequate explanation for folate deficiency in many patients with depression as several studies have failed to confirm this.¹ We have recently reported a fall in CSF folate with aging² and this may be a factor contributing to the high incidence of folate deficiency in psychogeriatric patients, including depression and dementia.¹ We have also reported a fall in CSF tetrahydrobiopterin (BH4) in depression which is correlated with folate deficiency, as reflected in a fall in red cell folate, and with impaired monoamine metabolism—that is, a fall in CSF monoamine metabolites.³

The mechanisms of these relations between impaired folate and monoamine metabolism remain uncertain but the suggestion that oxidative stress plays a part is speculative. We are unaware of any clinical or experimental evidence that oxidative stress leads to folate deficiency. It has been suggested that folates play a part in maintaining BH4 synthesis.^{3,4} The relation of folate and BH4 to aging requires clarification. It is also relevant that S-adenosyl-methionine, the major methyl donor in the brain which derives its methyl group from methyl folate can, like folates, increase the turnover of monoamines in the brain.⁵ This and other evidence suggest that methylation mechanisms are involved in these relations and in mood and cognitive function.⁶

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Long term follow up after perimesencephalic subarachnoid haemorrhage

Marquardt *et al* describe the clinical course and long term outcome of 21 patients they diagnosed as having a perimesencephalic haemorrhage.¹ The paper raises two questions.

The first is an impression of an "emperor's new clothes syndrome" given by the first figure of the publication. This figure shows a slice of the CT made shortly after the initial episode of headache in the patient reported to have a recurrent episode of perimesencephalic haemorrhage. The legend of the figure states that the CT shows extravasated blood in the perimesencephalic subarachnoid space, but we fail to see any blood at all. Thanks to the electronic availability of the *Journal* we were able to review not only the paper version of the figure, but also an enlarged version on screen. Even after enlargement no blood was seen; the slice nicely shows the tentorium adjacent to the ambient cisterns, the proximal parts of the posterior cerebral arteries, and perfectly clear CSF in the perimesencephalic (chiasmatic and partly the ambient and quadrigeminal) cisterns and in the frontal interhemispheric and sylvian fissures.

There are several explanations for this diagnostic mystery. Firstly, the authors may have submitted an inappropriate slice of the CT. In some patients with perimesencephalic haemorrhage, the prepontine cistern is the only site where CT shows blood.² If blood was visible in the prepontine cistern in this particular patient, the authors have indeed found a patient with a perimesencephalic, non-aneurysmal haemorrhage with a recurrent haemorrhage. Given the unique character of this sequence of events, it would be fair to provide the appropriate slice to convince readers of the *Journal*.

Secondly, if no evidence of blood is found even in the prepontine cistern, the patient may have had a CT negative subarachnoid haemorrhage. In patients with ruptured aneurysms CT can be negative, even if performed within 12 hours after onset of the haemorrhage.³ But a negative CT plus a negative angiography does not add up to a diagnosis of perimesencephalic haemorrhage.

Thirdly, the patient may not have had a subarachnoid haemorrhage at all. The case report tells us that lumbar puncture was positive, but does not give details. Because

lumbar puncture was performed before the CT, and CT was performed on the day of the headache, lumbar puncture may have been performed too early to detect blood degradation products in the CSF and therefore too early to distinguish a traumatic tap from a genuine haemorrhage. In the absence of degradation products the patient may have had a non-haemorrhagic cause of the headache.

With regard to figure 2, a slice of the CT made after the second episode of headache, it would be interesting to know the interval between the onset of symptoms and the CT. Perimesencephalic haemorrhage can be diagnosed reliably only if the initial CT is performed within 3 days after onset of the symptoms. After this interval distinction between aneurysmal and perimesencephalic patterns becomes unreliable.

The second issue is that of long term outcome. On long term follow up the authors found a high rate of persisting symptoms such as headaches, irritability, depression, and fatigability. This contrasts with the good quality of life (as measured by the sickness impact profile, a validated questionnaire on quality of life) found in a follow up study performed in The Netherlands.⁴ If the methods used by Marquardt *et al* are valid, the difference in outcome between these two study populations requires an explanation. This is where the question on management strategy for patients with perimesencephalic haemorrhage comes in. Do the authors include any restriction in counselling their patients who have had a perimesencephalic haemorrhage, or are such restrictions imposed on these former patients by physicians who assess people before employment or by medical advisors of insurance companies? We reassure patients on discharge and again a couple of weeks later, at an outpatients, consultation, that a perimesencephalic haemorrhage is not a warning for a major neurological event, we do not impose any restrictions, and we stimulate patients to take up all activities they undertook before the haemorrhage. We hypothesise that imposing restrictions or sharing uncertainties or worries with patients can lead to subjective symptoms as described above. Given this possibility we are reluctant to start informing patients that perimesencephalic haemorrhages can reoccur, as long as recurrences have not been reported convincingly. We do agree that the patient reported on forms a diagnostic challenge, but we have too little evidence to agree that this patient has had two episodes of perimesencephalic haemorrhage.

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The authors reply:

We respond to some of the questions raised by Rinkel and Velthuis on our recent publication in this *Journal*.¹ The patient of interest presented with typical clinical signs of subarachnoid haemorrhage. He complained of sudden onset of severe headaches, irradiation into the nuchal region, and nausea. Lumbar puncture was performed and blood stained CSF was found. Centrifugation of the CSF disclosed xanthochromia of the supernatant fluid and cytology demonstrated siderophages indicating the presence of intracranial haemorrhage as no lumbar puncture was carried out earlier.² Non-contrast enhanced CT showed blood in the ambient cisterns and these findings were interpreted as perimesencephalic subarachnoid haemorrhage in two different hospitals.

Four vessel digital subtraction cerebral angiography with multiple views was negative as was a repeated angiography 10 weeks later. A third angiography performed in the course of the second episode of haemorrhage again did not disclose any source of the bleeding, and thus the causes of bleeding remain unresolved. A recent publication by Canhao *et al* studied the prevalence of vascular risk factors in patients who had perimesencephalic subarachnoid haemorrhage.³ They found that hypertension was more frequent among patients with perimesencephalic haemorrhage than among two control groups and that among women, smoking was more common in perimesencephalic haemorrhage. However, the medical history of our patient was not relevant, and there was no history of previous arterial hypertension.

Rinkel and Velthuis express their concern about a high rate of persisting symptoms such as headaches, irritability, depression, and fatigability in long term follow up of our patients. They state that these findings contrast with the good quality of life found in a follow up study performed by Brilstra *et al*⁴ and that these differences require explanation.

In this study, which was cited by us as well, quality of life was measured by means of the sickness impact profile and outcome of patients with perimesencephalic subarachnoid haemorrhage was compared with that of a reference population. Analysing the submitted data, however, significant differences towards less dysfunction in patients were proved only for the categories body care, movement, and household management. Six of the 25 patients (24%) had more dysfunction in the category work than the reference population, and 11 patients (44%) reported a change in their headache pattern as non-specific headaches occurred more often than before the haemorrhage in 10 patients and less often than before in one patient. Two patients reported fear of rebleeding. Brilstra *et al* concluded that patients with a perimesencephalic haemorrhage have no reduction in quality of life but had to admit "that most consequences of the perimesencephalic subarachnoid haemorrhage are found in the psychosocial domains." They relate the problems with short term memory, sleeping, fears, irritability, and nervousness with the haemorrhage itself and with the experience of sudden illness leading to admission to an intensive care unit.⁴ These results imply that in the Dutch study as well persisting symptoms are frequent and this does not contrast with our findings at all. However, the focus of our follow up study

was directly on these psychosocial implications of perimesencephalic subarachnoid haemorrhage. Only 38% of our patients thought that they were fully recovered and completely well whereas 62% of the patients had residual complaints. Moreover, only 41% of the patients returned to their previous occupation whereas 53% of the patients retired from work and one man became unemployed. Thus quality of life after the haemorrhage is not as excellent as suggested and it becomes obvious that perimesencephalic subarachnoid haemorrhage has an enormous impact on individual patients and social life.

We do agree with Rinkel and Velthuis on the further management strategy for patients with former PMSAH. We inform the patients of the benign nature of the disease and do not impose any restrictions at all. We also reassure the patients that they can return to the same regular daily activities they undertook before the haemorrhage.

It is supposed that in 15% to 20% of the patients with subarachnoid haemorrhage the angiogram is negative and that patients with PMSAH account for about half of these patients with angiogram negative subarachnoid haemorrhage.⁵ On these premises there must be thousands of patients every year who are treated for PMSAH throughout the world. However, reviewing the literature in 1996, Schwartz and Solomon could only find 169 reported patients who had PMSAH.⁵ It seems, therefore, reasonable to compile more data to gain more information about the natural course of PMSAH in significantly larger cohorts of patients.

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Idiopathic intracranial hypertension and anticardiolipin antibodies

The study by Kesler *et al*¹ concludes with the assumption that the presence of anticardiolipin antibodies (aCL-Abs) indicates a unique subgroup of patients with idiopathic intracranial hypertension. Their study does not support this view. They regard as important in this respect the fact that the three patients with aCL-Abs ($p < 0.035$) were significantly older than those without. This is hardly surprising when it is known that the incidence of these antibodies increases with age and may be identifiable in up to 12% of healthy people.^{2,3} Their control group therefore needs to be age matched. Further speculation for