Enlargement of the third ventricle and hyponatraemia in aneurysmal subarachnoid haemorrhage

E F M WIJDICKS, K J VANDONGEN, J VANGIJN, A HIJDRA, M VERMEULEN
From the University Departments of Neurology, Rotterdam, Utrecht and Amsterdam; Department of Radiology, University Hospital Dijkzigt, Rotterdam, The Netherlands

SUMMARY Hyponatraemia following aneurysmal subarachnoid haemorrhage is associated with an increased risk of cerebral infarction. Whether the development of hyponatraemia was related to enlargement of the third ventricle on the admission CT scan was investigated in a consecutive series of 133 patients who were seen within 72 hours of aneurysmal haemorrhage. Hyponatraemia occurred significantly more often in patients with enlargement of the third ventricle (with or without dilatation of the lateral ventricles) than in patients with a normal ventricular system (20/41 versus 24/92, p = 0.016). After ventricular drainage, the sodium levels returned to normal in two patients in whom the size of the third ventricle decreased and not in four patients with persistent enlargement of the third ventricle. The significant relationship between enlargement of the third ventricle and hyponatraemia remained after adjustment for the amount of cisternal blood, but not after adjustment for the amount of intraventricular blood. These results suggest that the size of the third ventricle is an important but not the only factor in the relationship between acute hydrocephalus and hyponatraemia in patients with aneurysmal subarachnoid haemorrhage.

Hyponatraemia following aneurysmal subarachnoid haemorrhage (SAH) is not an infrequent finding and is associated with an increased risk of cerebral infarction. Hyponatraemia was previously attributed to an inappropriate secretion of antidiuretic hormone, but recently it was demonstrated that hyponatraemia is a result of salt wasting. What cerebral factor causes natriuresis after SAH remains to be established.

In a previous study, we found a relationship in patients with SAH between the development of hyponatraemia and the presence of hydrocephalus on admission. A possible explanation was that enlargement of the third ventricle might interfere with hypothalamic function. In that study, however, the width of the third ventricle was not measured, as the diagnosis of acute hydrocephalus was based on the width of the lateral ventricles. Therefore, the relationship between enlargement of the third ventricle and hyponatraemia was not investigated:

Patients and methods

The CT scans of 134 consecutive patients with signs and symptoms of a subarachnoid haemorrhage and with computed tomographic evidence of extravasated blood in the basal cisterns, suggesting a ruptured aneurysm were reviewed. Patients with causes other than a ruptured aneurysm or patients with a negative angiogram were excluded. CT scanning was performed on admission, always within 72 hours of the bleeding and was repeated weekly and after any clinical deterioration. An aneurysm was confirmed by angiography or postmortem examination in 99 of the 134 patients. In the remaining patients angiography was not performed because of age over 65 years or poor clinical condition.

In these patients the diagnosis was based on CT evidence only, particularly signs of blood in the basal cisterns and absence of patterns other than aneurysmal haemorrhage. This consecutive series of patients was part of a randomised, double-blind, placebo-controlled trial on the effectiveness of tranexamic acid. One patient died within 24 hours of massive intraventricular haemorrhage and was not included in the analysis. The remaining 133 patients were studied for a 4-week period after the presenting haemorrhage or until death or operation within this time. During this period all patients were under continuous observation in an intensive-care unit. Fifty two patients underwent surgical obliteration...
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of the aneurysm, mostly on the twelfth day after the presenting haemorrhage.

The width of the third ventricle on the initial CT scan was measured with a transparent ruler from X-ray films, and multiplied by the appropriate magnification factor (there were two CT machines) to obtain the real size. The slice where the third ventricle had the maximal transverse diameter was chosen. The normal values of the third ventricle were used as described by Meese.9 The upper limit of normal (90th percentile) was defined as: 5 mm at age 40 years or under, 6 mm at age 50, 7 mm at age 60 and 9 mm at age 80. The width of the third ventricle was converted into a relative size by dividing the width of the third ventricle by the upper limit for age.

The bicaudate index was defined as the width of the frontal horns at the level of the caudate nuclei, divided by the corresponding diameter of the brain. The bicaudate index was converted into a relative size by dividing the bicaudate index by the upper limit for age for each half decade (95th percentile) as previously described.5 At the time of measurement, the investigators had no knowledge of the clinical condition of the patients and, in particular, they were not aware which patients had developed hyponatraemia.

The amount of cisternal blood on the initial CT scan was separately graded for 10 cisterns and fissures. Patients were then distinguished into those with no cisternal blood or a small amount in only one cistern or fissure and those with frank cisternal haemorrhage. This dichotomy appeared to be related to the incidence of infarcts, according to our own data (to be published) and those of others.10,11

Similarly, the amount of intraventricular blood on the initial CT scan was graded separately for each ventricle, on a scale of 0 to 3. A total score of 2 usually represented sedimentation of red blood cells in the dependent parts of the ventricular system and only higher scores were regarded as frank intraventricular haemorrhage.

Hyponatraemia was defined as a sodium level lower than 135 mmol/l on at least 2 consecutive days, in the absence of hyperlipaemia or hypoproteinaemia.4 Serum sodium levels were measured on admission and at least three times a week.

CT scanning was repeated weekly and after each clinical deterioration. Cerebral infarction was diagnosed if (1) there were new focal signs or a decrease in level of consciousness, usually of gradual onset; and (2) CT showed a hypodense lesion compatible with the clinical signs, or there were no lesions other than infarction that could explain the clinical signs.

Results

In this series of 133 patients, the admission CT scan showed enlargement of the lateral ventricles and also of the third ventricle in 26 patients (20%), of the third ventricle only (fig 1) in 15 patients (11%), and of the lateral ventricles only (fig 2) in 3 patients (2%). Hyponatraemia developed in 44 of the 133 patients (33%), always between day 2 and day 10 (median: day 4) after the haemorrhage. It was mild (130 to 134 mmol/l) in 18, moderate (125 to 129 mmol/l) in 20 and severe (120 to 124 mmol/l) in six patients. Twenty six of the 44 patients who developed hyponatraemia were fluid-restricted as reported in detail before.1 Twenty of the 41 patients with an enlarged third ventricle on admission developed hyponatraemia, versus 24 of the 92 patients with a normal third ventricle (χ² test, p = 0·016). Figure 3 shows the relative size of the third ventricle in patients with and without hyponatraemia (Mann-Whitney, p = 0·05). There was no apparent linear correlation between the degree of hyponatraemia and the degree of ventricular enlargement (data not shown).

The incidence of hyponatraemia in the three groups of patients with hydrocephalus was compared with that in patients with normal ventricles (table 1). Hyponatraemia occurred more often in patients with enlargement of the lateral ventricles as well as with the third ventricle, and also in patients with isolated enlargement of the third ventricle. These differences did not reach statistical significance after corrections for multiple testing (Bonferroni method).12

The significant relationship between hyponatraemia and enlargement of the third ventricle
remained on separate analysis of the patients with marked hyponatraemia (sodium levels 120–130 mmol/l): 14 of the 26 patients with marked hyponatraemia had an enlarged third ventricle as opposed to 27 of the 107 patients with normal sodium levels or mild hyponatraemia (131–135 mmol/l) ($\chi^2$ test, $p < 0.01$). Serial CT scans were done in 113 patients. In 25 of the 44 patients the CT scan showed an enlarged third ventricle at the time of hyponatraemia compared with 26 of the 69 patients who maintained normal sodium ($\chi^2$ test, $p < 0.05$).

The relationship between enlargement of the third ventricle and hyponatraemia remained after adjustment for the amount of cisternal blood (Mantel-Haenzel test, $p = 0.02$ see table 2). In an earlier study, we also failed to find an association between the extent of cisternal haemorrhage and enlargement of the lateral ventricles.\textsuperscript{6} Frank intraventricular haemorrhage was found in 18 of the 44 patients with hyponatraemia versus 20 of the 89 patients with normal serum sodium levels (Fisher's exact test, $p = 0.02$). After adjustment for intraventricular haemorrhage, the association between enlargement of the third ventricle and hyponatraemia no longer reached significance ($0.05 < p < 0.10$; table 3). Intraventricular haemorrhage was in itself very strongly related to enlargement of the third ventricle (21/41 versus 17/92, $p < 0.001$; table 3).

Cerebral infarcts occurred more often in patients with enlarged third ventricles (18/41 = 44\%) than in patients who had a normal third ventricle (28/92 = 30\%). This difference did not reach statistical significance. Fatal infarcts were also more frequent in patients with enlargement of the third ventricle (9/41 = 23\%) versus 9/92 (10\%) in patients who had a normal third ventricle (not significant, $0.05 < p < 0.10$).

An aneurysm was demonstrated by angiography or at postmortem examination in 31 patients with hypo-

### Table 1 Correlation of ventricular size with hyponatraemia

<table>
<thead>
<tr>
<th>Ventricular size on the initial CT scan</th>
<th>Hyponatraemia</th>
<th>Normal serum sodium</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enlargement of third ventricle:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With enlarged lateral ventricles</td>
<td>12</td>
<td>14</td>
<td>26</td>
</tr>
<tr>
<td>With normal lateral ventricles</td>
<td>8</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>Normal third ventricle:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With enlarged lateral ventricles</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>With normal lateral ventricles</td>
<td>22</td>
<td>67</td>
<td>89</td>
</tr>
<tr>
<td>Total</td>
<td>44</td>
<td>89</td>
<td>133</td>
</tr>
</tbody>
</table>

Differences in different subgroups not significant after correcting for multiple testing.
natraemia. Of these, 13 had an aneurysm of the anterior communicating artery (42%), 11 of the carotid artery (35%), three of the middle cerebral artery (9%) and four of the posterior circulation (13%). For the 68 patients with normal sodium levels and a proven aneurysm, the distribution was similar: 26 (38%), 22 (32%), 13 (9%) and 7 (10%), respectively.

Nine patients with an enlarged third ventricle underwent ventricular drainage, six of whom had developed hyponatraemia. In four of these six patients the size of the third ventricle did not change after shunting, and hyponatraemia persisted. In the two other patients, both the size of the third ventricle and the sodium level returned to normal after ventricular drainage.

Discussion

The risk of developing hyponatraemia after SAH appears to be significantly increased in patients with enlargement of the third ventricle on the admission CT scan, with or without dilatation of the lateral ventricles. This suggests that the size of the third ventricle is the crucial factor in the relationship that was previously found between acute hydrocephalus and hyponatraemia. Furthermore, the relationship between hyponatraemia and an enlarged third ventricle holds at more marked hyponatraemia levels and after measurement of the third ventricle on serial CT scans during the presence of hyponatraemia.

The pathogenesis of hyponatraemia after SAH is not known. It has been suggested that the hypothalamus may be damaged by rupture of an aneurysm of the anterior circulation, and that this damage may result in disturbances of the electrolyte balance. However, we could not confirm that the aneurysms occurred at different sites in patients with or without hyponatraemia.

Another possibility is that hyponatraemia is caused by hypothalamic dysfunction secondary to spasm of vessels that supply the hypothalamus. Since vaso-spasm is often multifocal, it might, in this view, account for both hyponatraemia and cerebral infarction. If this hypothesis was true, an association between the amount of cisternal blood and hyponatraemia should be found, as cerebral ischaemia is associated with the amount of cisternal blood. However, after adjustment for the amount of cisternal blood, the relationship between enlargement of the third ventricle and hyponatraemia remained unaltered. In contrast, the significant relationship between enlargement of the third ventricle and hyponatraemia was weakened after adjustment for the amount of intraventricular blood. The direct contribution of intraventricular haemorrhage towards the development of hyponatraemia is, however, small, and the main effect of intraventricular blood is that it causes enlargement of the third ventricle which then results in hyponatraemia.

Now that it has been shown that enlargement of the third ventricle is an important factor in the development of hyponatraemia, with some contribution of intraventricular blood, a possible explanation might be that mechanical pressure on the hypothalamus from within the third ventricle is responsible for hyponatraemia. This is further supported by the observation that hyponatraemia persisted when ventricular drainage did not result in a decreased size of the third ventricle, whereas the hyponatraemia disappeared if the third ventricle did shrink. This is in agreement with an observation of Wise. In this report two patients developed hyponatraemia after obstruction of a previously placed ventriculo-atrial shunt, and the sodium levels again became normal following revision of the shunt.

Dysfunction of the hypothalamus might cause hyponatraemia in different ways. It was originally

<table>
<thead>
<tr>
<th>Table 2 Correlation of hyponatraemia with the amount of cisternal blood and enlarged third ventricle</th>
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<tr>
<td>Amount of cisternal blood</td>
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<td>---------------------------</td>
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<tr>
<td>Enlarged third ventricle:</td>
</tr>
<tr>
<td>Total cases</td>
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<tr>
<td>No. hyponatraemia</td>
</tr>
<tr>
<td>% hyponatraemia</td>
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<tr>
<td>Normal third ventricle:</td>
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<tr>
<td>Total cases</td>
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<tr>
<td>No. hyponatraemia</td>
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<td>% hyponatraemia</td>
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<td>Totals</td>
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<tr>
<td>No. hyponatraemia</td>
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<td>% hyponatraemia</td>
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<thead>
<tr>
<th>Table 3 Correlation of hyponatraemia with amount of intraventricular blood and enlarged third ventricle</th>
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<tr>
<td>Intraventricular blood</td>
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<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Enlarged third ventricle:</td>
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<tr>
<td>Total cases</td>
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<tr>
<td>No. hyponatraemia</td>
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<tr>
<td>% hyponatraemia</td>
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<tr>
<td>Normal third ventricle:</td>
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<td>Total cases</td>
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<td>No. hyponatraemia</td>
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<td>% hyponatraemia</td>
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thought that hypothalamic lesions might functionally isolate the osmoreceptors, which leads to an inappropriate and excessive ADH release. However, the recent findings of volume depletion and salt wasting in patients with hyponatraemia after SAH do not support this hypothesis. An alternative explanation for salt wasting after SAH is that dysfunction of the hypothalamus has an effect on the heart resulting in the release of the atrial natriuretic factor which in turn causes salt wasting in the kidney. Such a course of events might be related to changes in the heart that have been described after SAH. This hypothesis might be tested with the recently developed assays that detect the atrial natriuretic factor in plasma. Another possible explanation might be that pressure on the hypothalamus by the third ventricle causes the release of natriuretic peptides that are present in the anteroventral region of the third ventricle. Recently we demonstrated the presence of a digoxine like substance in the plasma of some patients with SAH, particularly in patients with a negative sodium balance. Finally, although enlargement of the third ventricle is important in the development of hyponatraemia, it is neither a necessary nor a sufficient factor, as half of the patients with hyponatraemia had a normal ventricular system, and half of the patients with an expanded third ventricle had constant levels of sodium. It might be that natriuresis does not always result in hyponatraemia.

Patients with SAH who develop hyponatraemia are at a greater risk of cerebral infarction. This was demonstrated earlier in the same group of patients, although fluid restriction was a confounding factor. Since hyponatraemia is caused by natriuresis and is accompanied by hypovolaemia, fluid restriction might have aggravated a hypovolaemic state resulting in ischaemia. The limits of our sample and the contribution of other factors in the pathogenesis of cerebral ischaemia may explain why a direct relationship between enlargement of the third ventricle and subsequent infarction could not be demonstrated. Nevertheless, the presence of a large third ventricle on the initial CT scan indicates that such patients are a greater risk of developing hyponatraemia and therefore need a careful control of the fluid and sodium balances to prevent cerebral ischaemia.

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Matters arising

McArdle’s sign in multiple sclerosis

Sir: Your readers may be interested in the background to the observation of increased pyramidal weakness with neck flexion in patients with spinal cord disease. This phenomenon was first brought to my attention in the mid-1960s by a patient with multiple sclerosis who was referred to me at the National Hospital, Queen Square. He had a marked spastic foot drop and had found that he could dorsiflex his foot if he fully extended his head.

I was able to confirm this observation and I also found that weakness of hip flexion, as tested by straight leg raising against resistance, which is usually the earliest sign of pyramidal weakness in the leg, was weaker on full neck flexion. I thought that this was the motor equivalent of Lhermitte’s sign and due to stretch of the spinal cord in full neck flexion.

The effect of neck movement is often slight and therefore, hip flexion should be tested with the neck in full flexion and in full extension to show the difference.

I subsequently tried this test on a large number of patients and found that it could occur in any condition affecting the spinal cord, although most easily demonstrated in multiple sclerosis. It may even be found in patients with lesions of the lower thoracic cord such as a thoracic meningioma as low as T11. I have observed it in patients with lesions at the foramen magnum, but not with lesions above this level. It is probably most useful in demonstrating weakness that would not otherwise be clearly evident.

References


Accepted 2 April 1988

Correction


Part of the last sentence of the second paragraph of the introduction was deleted. It should read “Therefore, the relationship between hyponatraemia and the size of the third ventricle was separately investigated”.

Reference