Cerebral circulation after head injury

Part 2: The effects of traumatic brain edema

Jørn Overgaard, M.D., and William A. Tweed, M.D.

Department of Neurosurgery, Odense University Hospital, Odense, Denmark

The authors have assessed the effects of subacute traumatic brain edema (BE) on cerebral circulation and metabolism, and on clinical outcome. Fifty-five severely injured, comatose, young patients who survived for more than 24 hours were studied on 78 occasions within 30 days of injury. After hematomas had been surgically evacuated, BE was diagnosed by radiological evidence of brain swelling, demonstrated by cerebral angiograms and ventriculograms. At identical levels of carbon dioxide pressure, intracranial pressure was significantly elevated in the Edema Group to twice the value in the No Edema Group (27.1 vs 14.1 torr). There were, however, no significant differences in cerebral perfusion pressure, cerebral blood flow, resistance to blood flow, cerebral metabolic oxygen rate, ventricular cerebrospinal fluid acid-base, lactate, K⁺ or Na⁺ concentrations, or in clinical outcome. It is concluded that this type of subacute traumatic BE, which is significantly associated with surgical lesions, is not of major hemodynamic or clinical significance in intensively treated patients, and does not cause cerebral ischemia. Patient outcome is determined more by the severity of the initial diffuse cortical and subcortical injury than by the presence or absence of subacute BE.

Key Words • head injury • coma • brain edema • cerebral blood flow • intracranial pressure

Clinical Material and Methods

Selection of Patients

Fifty-five children and young adults are included in this study; most were injured as the result of traffic accidents. All had clinical evidence of a diffuse disturbance of cerebral function with unconsciousness lasting from days to weeks, including those with focal lesions and hematomas who remained unconscious after operation. However, no attempt was made to assess BE prior to operation. Each patient was assigned to a neurological class on admission (A, B, or C).
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based on reliable clinical criteria which we have previously described as follows:25

Class A = unconscious with dilated fixed pupils
Class B = unconscious with abnormal motor patterns
Class C = unconscious with normal motor pattern.

Since most fell into neurological classes A and B (Fig. 1), indicating severe brain injury with a poor prognosis for recovery, we consider this a selected group of severely injured young patients. We did not include in the study patients who were either so severely traumatized that they died soon after admission to the hospital, or so slightly injured that they quickly showed clinical evidence of recovery.

Treatment

It is, of course, impossible to investigate the course of untreated BE in clinical studies. All patients in this study were observed and managed under intensive care. Our results, therefore, must be interpreted in this light, not as the natural course of clinical BE, but as the course of BE in vigorously treated patients who survived at least the first 24 hours after injury. Methods of treatment are listed in Table 1. The Edema Group and No Edema Group differed in only two respects; in the consequence of the time delay due to transport to the neurosurgical clinic, and in the incidence of surgical lesions and operations. Seventy-five percent of the patients were transported to the Odense Hospital from a referring hospital outside the city; the delay due to transport varied from 2 to 10 hours.

Before transportation, a clear airway was assured by intubation, and ventilation of the lungs was manually assisted. Cerebral angiography was performed in the neurosurgical clinic as soon as circulation and ventilation were stable, and hematomas were then surgically evacuated. All patients were sedated with phenobarbital, 150 to 400 mg/day, and measured serum levels were the same in those with and without BE (Table 1). Arterial carbon dioxide pressure (PaCO₂) was controlled for up to 2 weeks and maintained within the range of 30 to 35 torr; normal oxygen saturation was maintained. In some cases, an intraventricular catheter was inserted through a burr hole for measurement of ICP and evacuation of cerebrospinal fluid (CSF). Neither CBF studies nor classification of BE were done until the initial treatment had been completed.

Cerebral Blood Flow Studies

Fifty-five patients were studied on 78 occasions within 30 days after injury. Each study included measurements of CBF, mean arterial blood pressure (MABP), mean intraventricular pressure in the cerebral ventricles (MIVP), and blood gases. In most cases ventricular CSF was obtained and was analyzed for acid-base balance, lactate, and electrolytes. In 23 studies internal jugular venous blood was sampled and the cerebral metabolic rate for oxygen (CMRO₂) calculated.
TABLE 1

Comparison of treatment measures in patients in Edema and No Edema Groups

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total</th>
<th>Edema</th>
<th>No Edema</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>surgical lesion and operation</td>
<td>25</td>
<td>19 (76%)</td>
<td>6</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>contusion only (no operation)</td>
<td>30</td>
<td>10 (33%)</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>delay due to transport</td>
<td>41</td>
<td>26 (63%)</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>treated immediately</td>
<td>14</td>
<td>3 (21%)</td>
<td>11</td>
<td>p &lt; 0.02</td>
</tr>
<tr>
<td>artificial ventilation</td>
<td>37</td>
<td>19</td>
<td>18</td>
<td>NS</td>
</tr>
<tr>
<td>phenobarbital</td>
<td>55</td>
<td>2.86 mg%</td>
<td>3.38 mg%</td>
<td>NS</td>
</tr>
<tr>
<td>serum levels</td>
<td></td>
<td>±0.36</td>
<td>±0.34</td>
<td></td>
</tr>
<tr>
<td>ventricular CSF drainage</td>
<td>15</td>
<td>7</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>Decadron</td>
<td>12</td>
<td>6</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>mannitol</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Lasix</td>
<td>14</td>
<td>8</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>anti-hypertensives</td>
<td>10</td>
<td>7</td>
<td>3</td>
<td>NS</td>
</tr>
</tbody>
</table>

* The statistical significance of the differences was tested by the chi-square test.

Cerebral blood flow was measured by the intracarotid xenon injection method, recording the washout of xenon from the brain with 35 externally located scintillation detectors arranged in an array over the ipsilateral cranium. If there was a lateralizing abnormality or a surgical lesion, CBF measurement was made on the side of the lesion. We calculated CBF by two methods, the initial slope method, designated CBF\textsubscript{init}, and the 10-minute height over area method, designated CBF\textsubscript{lo}.\textsuperscript{23}

Regional values from each of the 35 separate channels were averaged to determine the average hemispheric value for CBF\textsubscript{init}; CBF\textsubscript{10} was calculated from the single washout curve obtained by continuously recording the average counting rate of the 35 channels. In the normal brain, CBF\textsubscript{init} is higher than CBF\textsubscript{10}, and is close to, but not identical with gray-matter flow.\textsuperscript{23}

In pathological states CBF\textsubscript{init} is linearly related to CBF\textsubscript{10} and measures perfusion in the high-flow tissues, primarily cortical tissue.\textsuperscript{25} On the other hand, CBF\textsubscript{10} is an approximation of mean tissue blood flow.

During each CBF measurement, MABP was continuously recorded from the carotid artery catheter and MIVP from a catheter inserted through a burr hole into a lateral cerebral ventricle. Cerebral perfusion pressure (CPP) was calculated as the difference between MABP and MIVP, and cerebrovascular resistance across the brain as CPP/CBF\textsubscript{10}.

An anaerobic sample of arterial blood was taken after each xenon injection and analyzed in a Radiometer gas analyzer\textsuperscript{†} for blood gases and acid-base. Ventricular CSF acid-base balance was determined from a sample of blood-free ventricular fluid withdrawn anaerobically from the ventricular catheter at the end of the CBF measurement. Samples contaminated with air or blood, and samples insufficient in amount were discarded. Cerebrospinal fluid lactate was measured by the method of Hohorst and Bergmeyer,\textsuperscript{5} and CSF electrolytes in a flame photometer.\textsuperscript{‡} We calculated CMRO\textsubscript{2} by multiplying the arterial jugular venous oxygen content difference by CBF\textsubscript{10}.

Classification of Brain Edema

The difficulties in clinical estimation of BE are well known.\textsuperscript{22} Because these patients were vigorously treated we felt that ICP alone was not a reliable indication of the presence or

\textsuperscript{†} Blood gas analyzer is manufactured by Radiometer, Copenhagen, Denmark.

\textsuperscript{‡} Flame photometer 343 is manufactured by IL Instrumentation Laboratory Incorporated, SPA Marketing of Sales, Via Rosellini 12, 20124 Milano, Italy.
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absence of BE. Therefore, at each study, cerebral angiography and ventriculography were performed through the catheters in the internal carotid artery and lateral cerebral ventricle. The diagnosis of BE was made in 29 patients solely on the basis of one or more of the following criteria: 1) dislocation of the midline structures (19 patients with hemispheric edema); 2) elevation of the middle cerebral artery group vessels (four patients); 3) compression of the cerebral ventricles to a “slit-like” appearance (three patients); 4) local dislocations of the ventricular wall (three patients: two with frontal edema, one parietal).

Since intracranial hematomas were always evacuated prior to the studies, we believe that focal or generalized swelling of the brain demonstrated in the above ways is due to BE. Patients with completely normal angiography and ventriculography were classified as having no edema. The validity of this classification will be discussed.

Classification of Clinical Outcome

All patients have been followed for periods ranging from 6 to 60 months after injury, and were placed in one of three previously defined outcome categories.

Category 1. These patients have functional recovery with or without slight deficits, with restoration of former social and economic capabilities (24 patients).

Category 2. These patients have severe neurological or mental deficits that clearly limit function. The best are capable of self care but are not self supporting; the worst require institutional supervision (14 patients).

Category 3. These patients have died or entered a vegetative type of survival (persistent vegetative state) (17 patients).

Results

Three conditions have been identified which are associated with an increased incidence of BE: patients with the most severe initial neurological injury (Class A on admission) all developed BE, in contrast to an incidence of 50% in Class B and C patients (p = 0.031). A 2- to 10-hour delay in neurosurgical treatment, occurring because of transport from an outlying community, was associated with a 63% incidence of BE, in contrast to an incidence of 21% in those arriving immediately (Table 1). Patients with delayed treatment often, on arrival, had untreated complications such as anoxia, hypercapnia, hypotension, and untreated surgical lesions.

After operation for a focal surgical intracranial mass lesion (epidural or subdural hematoma, intracerebral hematoma, or brain laceration with hematoma), there was a 76% incidence of BE, in contrast to an incidence of 33% in patients with contusion only (Table 1). The association of a surgical lesion with edema was particularly evident in the less severely injured (Class C) group; 100% of the nine patients in this class with edema had had an operated surgical lesion.

In all other respects treatment of patients in the two groups was identical (Table 1). The mean values for PaCO2 in hospital, the duration of artificial ventilation, and the serum phenobarbital levels were identical for both groups. We do not believe, therefore, that general treatment measures in the neurosurgical clinic influenced the recognition of BE, although we cannot be sure of their effect on its severity or rate of development.

Data concerning the hemodynamic and metabolic consequences of edema are presented in Table 2 and Fig. 2. The two groups were similar with respect to age, time from injury to study, and PaCO2 at the study. Although MIVP was not used in the classification of patients having “edema” or “no edema,” which was done solely on the basis of angiographic and ventriculographic findings, it was elevated in the Edema Group to twice the level found in the No Edema Group. Note that no attempt was made to diagnose BE preoperatively, but only after hematomas had been evacuated, lacerations revised, and tears in the dura closed. In view of these points, and the nearly identical values for PaCO2 in the two groups, it is most probable that this observed elevation of MIVP at the time of study was the consequence of traumatic BE. Despite this difference in MIVP the reduction of CPP in the Edema Group was not significant.

It is obvious that there was no difference in CBF in the two groups, whether measured as \( CBF_{init} \) or \( CBF_{io} \); it is also notable that these measures of CBF were less than 20% reduced from normal. There was also no difference in the incidence of focal-flow changes or “tissue peaks” between the two groups. Ischemic focal changes, that is, \( CBF_{init} \) reduced more...
TABLE 2
Comparative data in patients in Edema and No Edema Groups*

<table>
<thead>
<tr>
<th></th>
<th>Edema</th>
<th>No Edema</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean ± SD &amp; SEM</td>
<td>N</td>
</tr>
<tr>
<td>Patient's age (days from injury to study)</td>
<td>29</td>
<td>16.9 ± 7.3</td>
<td>26</td>
</tr>
<tr>
<td>PaCO2 (torr)</td>
<td>35</td>
<td>36.1 ± 6.7</td>
<td>43</td>
</tr>
<tr>
<td>MIVP (torr)</td>
<td>35</td>
<td>27.1 ± 22.8</td>
<td>43</td>
</tr>
<tr>
<td>CPP = MABP - MIVP (torr)</td>
<td>35</td>
<td>82.9 ± 28.0</td>
<td>43</td>
</tr>
<tr>
<td>CBF1init (ml/100 gm/min)</td>
<td>35</td>
<td>50.8 ± 17.8</td>
<td>43</td>
</tr>
<tr>
<td>CBF10 (ml/100 gm/min)</td>
<td>35</td>
<td>40.7 ± 10.8</td>
<td>41</td>
</tr>
<tr>
<td>CVR = CPP/CBF10</td>
<td>35</td>
<td>2.15 ± 0.76</td>
<td>41</td>
</tr>
<tr>
<td>CMRO2 (ml/100 gm/min)</td>
<td>11</td>
<td>1.05 ± 0.42</td>
<td>12</td>
</tr>
<tr>
<td>Lactate (mEq/l)</td>
<td>30</td>
<td>2.02 ± 0.13</td>
<td>34</td>
</tr>
<tr>
<td>pH</td>
<td>22</td>
<td>7.27 ± 0.06</td>
<td>31</td>
</tr>
<tr>
<td>pCO2 (torr)</td>
<td>22</td>
<td>50.5 ± 9.1</td>
<td>31</td>
</tr>
<tr>
<td>Potassium (mEq/l)</td>
<td>15</td>
<td>2.59 ± 0.03</td>
<td>23</td>
</tr>
<tr>
<td>Sodium (mEq/l)</td>
<td>14</td>
<td>148.7 ± 8.6</td>
<td>23</td>
</tr>
</tbody>
</table>

* N = number of measurements of each variable. SD = standard deviation; SEM = standard error of the mean. The statistical significance of the differences was tested by the t-test for unrelated samples. Normal values for adult humans, for comparison, are mainly from our laboratory (CBF1init = 58.7 ± 6.7, CBF10 = 46.8 ± 3.6, CMRO2 = 3.0-3.5, lactate = 1.2-1.5, pH = 7.31.

than 20% from the hemispheric average, were very infrequent, not related to the areas of BE, and not different in the two groups.

Cerebral metabolism, as assessed by CMRO2, was severely but equally reduced in both groups to 30% to 40% of normal. Global CBF, therefore, was adequate when related to the low levels of metabolism; in fact there is a relative global hyperemia or "luxury perfusion."\(^{17}\) Comparison of ventricular CSF levels of lactate, acid-base balance, and electrolytes revealed no difference between the two groups, no metabolic evidence for cerebral ischemia in either group, and little difference from normal values.\(^{19}\)

An attempt to grade BE into "severe" and "mild" grades based on differences observed in a single measurement of MIVP has not been possible and no significant differences in macroscopic injury, hemodynamics, metabolism, or clinical outcome could be determined. We have, therefore, abandoned clinical attempts to grade BE on the basis of ICP.\(^{32}\)

In Fig. 1 we see that when we examine clinical outcome in patients who were in the same neurological class when admitted, there is no significant difference between the Edema and the No Edema Groups. This suggests then, that the initial injury and not
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**FIG. 2.** Cerebral blood flow and pressures in patients with and without traumatic brain edema. The bar graphs illustrate data shown in Table 2.

Macroscopic BE is the primary determinant of outcome, particularly when one looks at clinical mortality (dead or vegetative) vs survival (with and without deficits).

**Discussion**

Experimental studies support the concept of two types of BE following injury. Cellular swelling (cytotoxic edema) is an immediate response to a neuronal injury, whereas extracellular edema (vasogenic edema) is a delayed phenomenon resulting from vasomotor disturbances, breakdown of the blood-brain barrier, and loss of autoregulation. Vasogenic BE is, as well, augmented by arterial hypertension.

The clinical counterpart to experimental vasogenic edema is probably an increased volume of extracellular fluid in the telencephalic white substance, resulting in reduction of the available free intracranial space, with a decrease in size of the ventricles and progressive obliteration of the subarachnoid space. In the case of unilateral edema, a shift of the midline vessels and brain septa occurs, while local displacements of brain vessels or indentations of parts of the ventricular system will reflect regional increases of brain bulk. In experimental studies, these displacements have been related to increased content of water in white matter. After an experimental lesion, this type of BE develops within a few hours and during this time is associated with pressure gradients within the brain. After an experimental cortical injury, the direction of bulk-fluid movement is from the cortex into the extracellular white substance of the centrum semiovale, and the measured water content of cortical gray matter is mainly unchanged.

The clinical problem of diagnosing traumatic BE can only be solved indirectly since neither regional measurements of ICP nor brain biopsies are feasible. Indirect measurements of brain swelling, such as angiography and ventriculography, may be acceptable provided traumatic hematomas have been evacuated and no enlarged subdural space is present. However, exact localization of the increase in brain bulk
between the "inner plate" of the cortex and the ventricular ependyma cannot be made. These increases in brain bulk should be termed edema and not contusion for the following reasons. Brain contusion is defined as "minute disperse intracerebral bleedings without disruption of the outer continuity of the brain; . . . and with blood in the cerebrospinal fluid. . . . contusion is invariably accompanied by edema which may be the more important lesion as far as symptoms and recovery are concerned." Although ventricular CSF was initially bloody in most cases, it was free of gross blood by the time of CBF study. The mass lesions we call BE developed after the initial angiography that was done to diagnose surgical lesions. These surgical lesions, including gross intracerebral hematomas, had been evacuated. We think, therefore, that the brain swelling that we saw at the CBF studies should be properly termed BE, not contusion.

These criteria for diagnosing traumatic BE do not entirely exclude edema when no displacement is seen, as visible displacement certainly requires a finite volume of filtered fluid, nor is cytotoxic edema taken into account. For the sake of clarity we have, however, classified patients with normal angiograms and ventriculograms as having "no edema." Positive radiological evidence of BE was found within a few hours after injury and occasionally as late as 31 days. In some cases, BE progressed while the patient's state improved, even after consciousness was regained. In most cases, the evidence of BE had disappeared by 3 weeks after injury. It is evident, therefore, that there is no animal model at present that mimics this clinical picture of traumatic BE. No relationship could be established between the time course of BE and the clinical state of the patient.

Cerebral ischemia may occur with large compressive extracerebral lesions, and when ICP is elevated to near the level of arterial blood pressure. We have not included studies of either, and have in fact studied only a few patients with the latter problem, most of whom died soon after injury. It is also accepted that traumatic BE may cause increased ICP and ischemic cerebral perfusion. This study confirms that ICP is higher when BE is diagnosed, but even in the No Edema Group it is probably not entirely normal. It is relevant that Nakatani and Ommaya have demonstrated that slowly increasing intracranial volume may reach the lethal level with only a slight increase in ICP, and that the level of ICP depends not only on that volume but also on its rate of accumulation. We have not studied fulminating, rapidly lethal brain swelling, but "subacute" BE development, which seems to progress more slowly. Because this is slowly accumulating BE, its extent cannot be reliably assessed by the level of ICP, which may partly explain our inability to grade severity on the basis of ICP.

The level of ICP after brain injury is affected not only by the amount of BE fluid and its rate of accumulation, but also by several other factors. Hypercapnic vasocongestion was controlled in these patients, and in no case was angiographic venous obstruction demonstrated. It is more difficult, however, to assess or control passive vasocongestion due to loss of autoregulation and fluctuating hypertension. One sign of vasomotor instability is spontaneous pressure waves, but these are reduced by controlled hyperventilation, and were only observed once in 380 hours of recording.

Changes in the rates of CSF absorption have not been assessed. Increased absorption may account for the occasional observation of normal ICP with pronounced radiological brain swelling, and impairment of absorption may explain the occasional increase in ICP with normal radiological findings. It is clear, therefore, that the amount of BE cannot be simply related to the level of ICP. The circulatory and metabolic effects of this type of BE in intensively treated patients, are slight and we have found no evidence for either diffuse or regional cerebral ischemia or cerebral hypoxia in these studies.

Resistance to blood flow (CVR) was not increased in patients with BE, and so it appears that BE per se has little effect on tissue microcirculation. This fact contradicts the findings of Bruce, et al., who have suggested that "focal edema may cause a regional decrease in CBF through compression of the microcirculation." Even in cases with hemispheric brain swelling, we have not observed an increase in CVR. The modest reduction of CBF in our patients was associated with a marked decrease in CMRO₂, and so an uncoupling of the normal metabolic control of CBF was evi-
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dent. There was no greater incidence of focal changes in Edema Group patients, and no ischemic focal changes in the cortical CBF over the edematous areas. We cannot, therefore, support the concept that BE impairs microcirculatory blood flow. Cerebral perfusion, then, should be well maintained as long as CPP is adequate, that is, if marked rises of ICP are prevented. This can only be done if ICP is effectively monitored. It is most probable, however, that the lethal effects of progressing BE are in most cases due to dislocations of the brain, transtentorial herniation, and compression of telencephalic and brain-stem structures rather than to supratentorial hemispheric ischemia.

When clinical recovery is examined in patients from the same initial neurological class (Classes B and C), there is no difference in clinical mortality (dead and vegetative) due to BE. We conclude that we are studying subacute regional BE in most cases associated with a focal surgical lesion, particularly in the less severely injured. This type of BE, if adequately treated, follows a more benign course than the diffuse, acute, fulminating, rapidly lethal brain swelling that follows the most severe injuries. This does not, however, explain the occasional clinical observation of "secondary brain injury," that is, progressive, diffuse, and often lethal brain swelling in a patient initially only slightly injured. These cases are, in our experience, unusual, and we have not had the opportunity to study one.

This study supports our concept that the age of the patient and the severity of the initial diffuse cortical and subcortical neuronal-glial injury are the primary determinants of clinical recovery after head injury, although the relative distribution of the immediate injury to cortical and white substance cellular elements still remains unclear. This strongly suggests that if further progress is to be made in the treatment of head injury, we must concentrate upon the period immediately following the injury, at the scene of the accident, during transport to hospital, and the initial minutes or hours in the hospital emergency room.

Acknowledgment

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Address for Dr. Tweed: Department of Anesthesia, Health Sciences Center, 700 William Avenue, Winnipeg, Canada.

Address reprint requests to: Jørn Overgaard, M.D., Department of Neurosurgery, Odense University Hospital, DK-5000, Odense, Denmark.