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Altered Mental Status

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Although the majority of alterations in sensorium in cancer patients are caused by endogenous or exogenous intoxication, the clinician must be alert to the possibility of structural disease in any patient who experiences a change in mental status. Accurate diagnosis of structural disease and prompt intervention can significantly improve the outcome of cancer treatments.

Mogami et al. (1983) note five causes of increased intracranial pressure due to structural lesions in cancer patients: *(1)* intracranial space-occupying lesions, especially malignant tumors; *(2)* leptomeningeal tumors; *(3)* hemorrhage into brain tumors; *(4)* intracranial hemorrhage due to hemorrhagic diathesis related to malignant tumors; and *(5)* cerebral thrombosis or embolism due to an increase in blood coagulability caused by malignancy. Raised intracranial pressure may also occur as a complication of nonstructural conditions such as chronic infectious meningitis (Wilhelm and Ellner, 1986) the encephalitides, and severe metabolic disturbances such as hepatic encephalopathy, respiratory failure, and exogenous intoxications.

Ironically, severe intracranial hypertension may accompany treatment of intracranial metastases, especially tumors that are sensitive to therapy. This commonly occurs with radiotherapy, including radioisotope therapy (Datz, 1986) for sensitive tumors. Cerebral herniation, which leads to increased intracranial pressure, is a possible, but uncommon complication of systemic chemotherapy (Walker et al., 1988) and cytokine treatment (Goey et al., 1988). Herniation has also been described as a complication of photodynamic therapy (Ji et al., 1992) for experimental gliomas. Patients with occult brain metastasis are in particular danger during the initiation of cytoreductive therapy. When the malignant cells are injured by therapy, they swell and induce edema in the surrounding tissues, thereby increasing intracranial pressure.

PATHOPHYSIOLOGY

Altered consciousness is caused by dysfunction in cerebral hemispheres, the diencephalon, or the tegmentum. The most minimal lesions producing altered consciousness are those affecting the posterior hypothalamus, midbrain, or cephalad brain stem. The pace with which a lesion develops influences the degree of altered function produced. Rapidly developing lesions such as arterial hemorrhage or embolic stroke produce greater deficits for the same volume of injury than more slowly evolving pathologies such as subdural hematoma or tumor (Plum and Posner, 1982).

Unilateral hemispheric disease alone does not alter consciousness (Haerer, 1992), but it may do so by *(1)* increasing intracranial pressure enough to cause dysfunction to both cerebral hemispheres; *(2)* causing sufficient inequalities in intracranial compartment pressures to provoke ischemia and herniation of vital neuronal arousal systems; or *(3)* blocking cerebrospinal fluid pathways, which leads to acute hydrocephalus, brain edema, diminished arterial flow, and, ultimately, bihemispheral dysfunc-

tion. In any one instance of altered consciousness due to a mass lesion, multiple mechanisms are almost always in effect.

EXAMINATION

Lundberg's literature review of case reports of intracranial space-occupying lesions and increased intracranial pressure lists 50 associated signs and symptoms (Lundberg, 1960). Many of these symptoms are nondescript, such as headache or dizziness, and can challenge diagnostic acumen. Symptoms such as visual obscurations, neck pain, or restlessness are liable to be overlooked by clinicians, particularly if intracerebral lesions are not expected.

The neurologic examination of the comatose patient allows the clinician to chart central nervous system (CNS) physiology from moment to moment. Computerized tomography and magnetic resonance imaging (MRI) scans or neurophysiologic monitoring cannot replace skilled observation by the caretakers of comatose patients. The patient's eye movements and pupils tell a great deal about the integrity of diencephalic and brain stem structures critical to the maintenance of consciousness (Fisher, 1969) and are briefly reviewed.

Pupillary light reaction should be checked in a darkened room for the rate of constriction and symmetry of reaction between the two eyes. Asymmetric, sluggish reaction of a pupil before dilation can alert the clinician to early tentorial herniation. Examination of the extraocular movements by oculocephalic reflex or caloric testing establishes whether diencephalic and brain stem structures adjacent to the alerting network of the reticular activating system are functioning normally. Oculocephalic (doll's eyes maneuver) testing is performed by slowly turning the patient's head from side to side and observing how the eyes respond. Normally, the eyes move conjugately in a direction opposite to that in which the head is turned. The eye movements in response to head turning should be unambiguously recorded.

A more reliable bedside examination of mesial rhombencephalic physiology is caloric testing, which is performed by placing the patient's head at approximately 30 degrees and gently irrigating the external auditory meatus with approximately 50 ml of ice-cold water over a span of a few minutes. The ear canals and tympanic membranes should be examined with an otoscope before irrigation to ensure that the tympanic membrane is intact and that there is no evidence of infection. Cerumen impaction should be cleared if it obstructs the external auditory meatus. Ice-water irrigation should be avoided if the patient is conscious, as it will precipitate unpleasant vertigo. The normal response is bilateral conjugate deviation of both eyes toward the ear receiving the ice water after a latent period of a few seconds. Pupillary and caloric testing are extremely resistant to metabolic disturbance, and abnormalities of these examinations argue strongly for structural disease in the midbrain or brain stem, although focal brain stem findings may rarely occur in patients with severe metabolic derangement.

Posturing of the limbs, either decorticate (arms flexed, legs extended) or decerebrate (arms and legs extended), is an ominous sign seen in severe midbrain dysfunction. Paroxysmal posturing is often mistaken for seizure, even, at times, by experienced clinicians. Abnormalities of tone, posturing, and Babinski's reflex may be seen in metabolic disturbance and on occasion asymmetrically in patients with underlying cerebrovascular disease or diabetes mellitus. When these symptoms are found, the patient should be urgently evaluated for the presence of an expanding intracranial mass. These signs implicate structural disease as the cause of altered consciousness, particularly when they are asymmetric or occur in association with abnormalities of ocular motility or pupillary reflexes.

BRAIN EDEMA

The presence of a mass lesion in the cranial vault increases intracranial pressure because of the incompliant nature of the skull to an expanding space-occupying lesion. The edema such a mass may induce in the surrounding brain can contribute to increased intracranial pressure to a much greater extent than the volume added by the tumor itself. Small tumors may cause massive edema (Fig. 25–1), and large tumors may cause only slight edema. On occasion, the tumor induces edema rapidly after a period of relatively harmonious co-existence, as if the relationship between the tumor and the surrounding normal brain tissue had suddenly been disturbed. Metastatic renal cell carcinoma and melanoma seem particularly capricious in this regard.

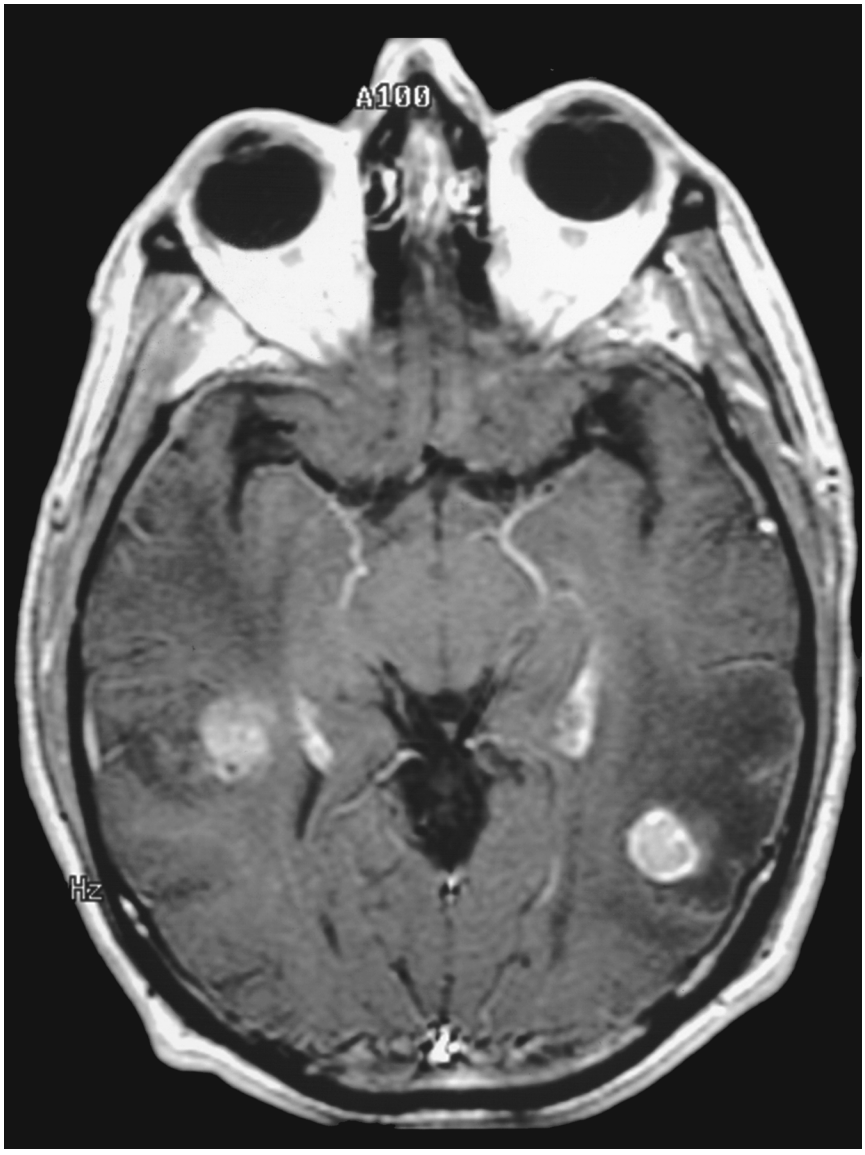

Figure 25–1. Magnetic resonance imaging scan of patient with bilateral brain metastasis from non–small cell lung cancer who presented with progressive headache and somnolence. Note the relative sizes of the tumors and the surrounding edema. Both metastatic deposits were resected, and the patient enjoyed improved function as a result.

Pathophysiologic Considerations

Brain edema is defined as an increase in water content per unit volume of brain parenchyma. Brain edema mechanisms are classically divided into three categories: cytotoxic, vasogenic, and interstitial (Klatzo, 1967). Cytotoxic edema is caused by noxious injury that produces cellular swelling and subsequent water increase in the intracellular compartment. Vasogenic edema is due to the release of water and solute from the intravascular compartment into the brain's interstitial space. Interstitial edema occurs when a hindrance to cerebrospinal fluid reabsorption increases intraventricular pressure enough to result in transependymal reabsorption of water and sodium into the brain's periventricular interstitial space (Fishman, 1975). In most

clinical situations, more than one mechanism contributes to brain edema.

Understanding the relationship between a lesion and the surrounding normal brain parenchyma is critical to any appreciation of the forces at play in producing intracerebral edema. The blood–brain barrier's integrity, dependent on the dynamic interaction of astrocytes, cerebral endothelium, and cerebral interstitium, plays a major but not exclusive role in the development of brain edema. Instances of relatively pure cytotoxic edema, such as may be seen following anoxic injury, produce swelling despite a closed blood–brain barrier. In anoxia the brain suffers swelling of all cellular components with resultant shrinkage of the extracellular space (Tommasino, 1992). In contradistinction, vasogenic edema results from an open (or leaky) blood–brain barrier that is associated with extravasation of plasma water, crystalloid, and colloid.

Factors at play in the production of brain edema can be better understood by applying the principles expressed by the Starling equation for fluid flow into interstitial tissues across a capillary vessel wall (Klatzo 1987). In this special case,

$$flow = K_f(\Delta P - \Delta\pi)$$

where K_f is the water conductivity of the capillary membrane and ΔP and $\Delta\pi$ are the differences between plasma and interstitial tissue hydrostatic pressure and plasma and interstitial tissue oncotic pressure, respectively. The differences between plasma and interstitial tissue hydrostatic pressure and between plasma and interstitial tissue oncotic pressure provide the motive force for fluid flow. This equation reveals that water conductivity of the capillary endothelial membrane, which is directly related to capillary permeability, is the greatest determinant of fluid flow when hydrostatic pressure and oncotic pressure remain relatively constant, as is the case in most acute clinical situations.

That the water conductivity of capillary endothelium does not depend exclusively on interruption of the blood–brain barrier is demonstrated by the fact that the area of brain edema surrounding tumor deposits frequently exceeds the nidus of contrast enhancement associated with the mass. Some of the edema may reflect locally increased oncotic pressure due to fractionation of proteins and peptides leaked from the region of blood–brain barrier breakdown (Rasmussen and Klatzo, 1969). Diffusion of these protein fragments and the resultant shift in oncotic forces likely plays a particularly important role in edema formation around tumors, especially those lesions associated with necrosis.

In addition to the increase in interstitial oncotic pressure from peptide leakage, brain edema surrounding tumor is affected by a host of vasoactive substances released from injured adjacent parenchymal tissue or from the tumor itself. Important among these substances may be the arachidonic acid metabolites (Yen and Lee, 1987), especially leukotrienes and prostaglandins, which are formed by the action of phospholipases from the tumor, and inflammatory cells (Aktan et al., 1991) on the rich lipid stores of the CNS. Elevated levels of leukotriene C4 are found in glioblastoma multiforme lesions as well as in the surrounding edematous tissue (Black et al., 1986). Corticosteroids suppress this edema mechanism through induction of a phospholipase inhibitor (Flower and Blackwell, 1979).

Brain tumors promote the production of numerous other factors that increase vascular permeability (Bruce et al., 1987). Inflammatory substances thought to be involved in brain tumor edema formation include histamine (Kolb, 1991), serotonin (Makarov et al., 1991), prostacyclin (Butti et al., 1991), thromboxanes (Gaetani et al., 1991), kallikrein-kinin (Maier-Hauff et al., 1984), glutamate (Baethmann et al., 1989), and other permeability factors (Ohnishi et al., 1990; Bruce et al., 1987) whose roles are as yet incompletely defined. The large number of inflammatory factors implicated in brain edema reflects the brain's enormous inherent inflammatory capability, particularly once the blood–brain barrier has been breached or when the inflammatory stimulus resides in the interstitial or subarachnoid space.

The brain has no inherent lymphatic drainage system, but the subarachnoid space serves as an efficient conduit for local wastes and nutrients. The free flow of fluid through the Virchow-Robin spaces, investitures of subarachnoid space that surround small arterioles for a short distance as they enter the brain, permits such rapid movement of even large protein molecules that it can be considered the "third circulation" (Cushing, 1926) for the CNS. Horseradish peroxidase injected into the subarachnoid space rapidly disperses throughout the cerebral interstitium but is largely excluded from regions of vasogenic

edema (Blaumanis et al., 1990). Ironically, regions where the blood–brain barrier is disturbed release vasoactive substances into the interstitium but flush out fewer of these noxious substances than the normal parenchyma does, reinforcing the development of edema.

Vasogenic edema mostly spares gray matter, with white matter bearing the brunt of the increased water and sodium content. The brain's white matter is largely composed of axons running parallel to one another that serve as orderly conduits for edema fluid. In contrast, the gray matter's neuropil forms a feltwork mesh that presents a relative impediment to interstitial fluid flow (Klatzo, 1987). Thus, vasogenic edema typically affects gray matter less than white matter. In a cat plasma-infusion model of vasogenic edema, cerebral blood flow did not change in edematous white matter, but the cerebral metabolic rate for glucose was significantly increased (Sutton et al., 1989). Vasogenic edema induces local anaerobic metabolism and local lactate production.

HYDROCEPHALUS

Cerebrospinal fluid is continuously formed, primarily by the choroid plexus in the lateral and fourth ventricles. Cerebrospinal fluid is secreted at a rate of about 0.35 ml/minute or 500 ml/day. The combined ventricular and subarachnoid cerebrospinal spaces have a capacity of about 150 ml, so the cerebral spinal fluid is turned over about three times a day (Rowland et al., 1991). Cerebrospinal fluid reabsorption occurs at the pacchionian granulations that are located over the cerebral convexities adjacent to the superior sagittal sinus, into which they drain. The pacchionian granulations, also called the *arachnoid villi,* function as valves that allow for unidirectional flow of cerebrospinal fluid from the subarachnoid space into the venous system. All components of the cerebrospinal fluid, including red blood cells and even microbes, can clear the cerebrospinal fluid and enter the blood stream through this bulk-flow drainage system.

Intracranial volume remains constant within the confines of the rigid outer skull. The intracranial volume is equal to the combined volumes of the brain, the intracranial blood, and the cerebrospinal fluid. When cerebrospinal fluid production exceeds cerebrospinal fluid absorption (removal), hydrocephalus results with consequent increases in intraventricular volume and intracranial pressure. Magnetic resonance imaging has shown that, under normal circumstances, caudal movements of the basal ganglia and pons as great as 1.5 mm may be seen during each normal systolic addition of about 100 ml of arterial blood to the closed system (Greitz et al., 1992). When transependymal flow of fluid occurs during hydrocephalus, these physiologic excursions may become exaggerated and contribute to the risk of herniation, particularly if there is an associated mass lesion.

Cerebrospinal fluid rarely causes hydrocephalus in cases of choroid plexus papilloma; the vast majority of hydrocephalus cases are due to impediment of cerebrospinal fluid drainage. Blockage of flow through this system produces progressive enlargement of the proximal ventricles because of the continual production of cerebrospinal fluid. Obstruction to flow can occur at the level of the pacchionian granulations, in which case all of the ventricles are in communication with one another and all are enlarged. The causes of communicating hydrocephalus include subarachnoid hemorrhage, meningitis, and grossly elevated cerebrospinal fluid protein.

INCREASED INTRACRANIAL PRESSURE

Whether the cranial vault pressure increases because of the growth of a mass within it (tumor, hemorrhage, or abscess), the development of hydrocephalus, or brain edema, the consequences are similar (Cushing, 1902). Although for over 200 years experimental evidence has demonstrated that elevated intracranial pressure alone is sufficient to cause coma, the mechanisms by which physiologic dysfunction arises are still being elicited. Table 25–1 summarizes many of the factors affecting intracranial pressure. The history of studies on cerebral dysfunction caused by elevated intracranial pressure has been admirably reviewed by Lundberg (1960) in his important monograph on human ventricular pressure monitoring.

If intracranial pressure increases above arterial pressure, tachycardia ensues, and the respiratory rate decreases. The brain consumes 15% of the cardiac output, and it is exquisitely sensitive to ischemia. White matter is more sensitive to ischemic damage, probably because white matter receives about 25%

Table 25–1. Factors Affecting Intracranial Pressure

Increased intracranial pressure
Hypercapnia (any degree)
Hypoxia (Pao_2 <50 mm Hg)
Hyperthermia
REM sleep
Halothane
Nitrous oxide
Decreased intracranial pressure
Hypocapnia (any degree)
Hyperoxia (Pao_2 >1000 mm Hg)
Hypothermia
Barbiturates
Narcotics
Muscle relaxants

Source: Modified from North and Reilly (1990).

less blood flow per unit volume of brain than the more metabolically active gray matter.

The cerebral arterioles are the main resistance vessels, rapidly responding to alterations in systemic blood pressure, pH, and Pco_2. Cerebral arterioles constrict when systemic blood pressure increases and dilate when it decreases, serving to maintain a relatively constant rate of cerebral blood flow. The cerebral arterioles are profoundly affected by changes in arterial CO_2 tension. Breathing 5% CO_2 increases cerebral blood flow by 50%, and breathing 7% CO_2 doubles it (Brust, 1991). A series of animal experiments have demonstrated that cerebral blood flow changes by 2% to 4% for each 1 mm Hg change in arterial CO_2 pressure (Harper and Glass, 1965). Similarly, acidosis increases cerebral blood flow and alkalosis decreases it.

Hypothermia lowers intracranial pressure by diminishing cerebral blood flow and protects neurons from ischemic injury by simultaneously lowering neuronal oxygen requirements. Unfortunately, rebound-raised intracranial pressure during rewarming limits hypothermia's clinical benefit.

Hyperthermia, on the other hand, increases intracranial pressure (Malkinson et al., 1985, 1990), with the chill phase causing the greatest rise in pressure. Heating experiments with normal rhesus monkeys, cats, and rats (Meyer and Handa, 1967) demonstrated a steady increase in cerebral blood flow, expired CO_2 content, and rate of cerebral metabolism of oxygen up to a temperature of 42°C, at which point metabolic activity and blood flow rapidly decline. In these experiments, the cerebral blood flow increased by 50% and the cerebral oxygen consumption by 33%. In an injured brain, the effects are even more profound. In one experiment, monkeys with cold-induced edematous brain lesions were warmed on heating blankets to 40°C. After only 2 hours at this temperature, they suffered 40% edema increases in the lesions (Clasen et al., 1974). On the basis of results of these and other experiments, it should not be surprising that hyperthermia can be catastrophic for patients with increased intracranial pressure. These patients should be aggressively treated with antipyretics and cooling blankets if necessary.

Critical to understanding the mechanisms by which tumors cause increased intracranial pressure is an understanding of the changes in local autoregulation wrought by pathologic tumor arterioles. In a cat xenotransplantation tumor model (Okada et al., 1992), clear correlation was noted between tumor pH decline and increased water content, whereas in peritumoral edema pH increased because of the efflux of alkaline lactate salts from the tumor into surrounding tissues. Such alterations in regional metabolism favor decreased peritumoral blood flow and diminished clearance of edema-associated molecules from peritumoral tissues by the circulation. This serves to maintain edema if the offending lesion is not removed.

Of the intracranial components, blood is the most labile. Under normal conditions, there is about 100 ml of blood in the cranium. Seventy percent of this volume resides in the venous system and its plexi, forming a high-capacity volume buffer against the vagaries of alterations in cerebral venous return to the systemic circulation. Change in venous return from the skull, which can be caused by respiratory fluctuations in thoracic pressure and their consequent effect on jugular venous pressure, congestive heart failure, or the superior vena cava syndrome, may have profound effects on intracranial pressure. Once venous capacity mechanisms are overwhelmed, intracranial pressure may rise dramatically.

When he monitored direct intracranial pressure in brain tumor patients, Lundberg (1960) observed waves of pressure increase that could be used to predict functional decompensation and herniation. These pressure waves ranged from 50 to 100 mm Hg and lasted 5 to 20 minutes. The waves reflect changes in

cerebral compliance and cerebrovascular capacity associated with increased intracranial pressure. Common signs and symptoms during sustained pressure waves include headache, neck pain, head noises, disordered consciousness, confusion, restlessness, rigidity of the arms, legs, or neck, clonic movements of the arms, bradycardia and hypertension (the Cushing response), hyperpnea, air hunger, nausea and vomiting, flushing of the face, sweating, urge to micturate, and itching of the nose. Unfortunately, the clinical syndrome is highly variable, and detection demands diligent observation by all who care for patients with increased intracranial pressure.

HERNIATION SYNDROMES

The brain's delicate structure and functional integrity are based on precise architectural relationships. Herniation disturbs these relationships and produces severe dysfunction. Table 25–2 summarizes symptoms commonly seen with cerebral herniation.

The commonly encountered herniation sites are *(1)* the mesial temporal lobes at the tentorial notch (uncal herniation), *(2)* the cerebellar tonsils through the foramen magnum, and *(3)* the cingulate gyrus of the frontal lobes underneath the cerebral falx. Less frequently, a central herniation syndrome may occur in which both mesial temporal lobes compress diencephalic structures. This syndrome is heralded by the midbrain tectal signs of bilateral ptosis and paresis of upward gaze (North and Reilly, 1990). Brain may herniate through a craniotomy site.

Table 25–2. Symptoms Associated with Cerebral Herniation

Headache, neck ache
Blurring of vision, amaurosis
Abducens paresis
Restlessness
Confusion
Rigidity of the neck
Opisthotonos, trismus
Rigidity and tonic extension or flexion of arms and legs
Bilateral extensor responses of plantar reflexes and other signs of spinal automatism
Cardiovascular disturbances
Respiratory disturbances
Rise in temperature
Nausea, vomiting
Hiccups

Table 25–3. Signs and Symptoms of Temporal Lobe Herniation from Supratentorial Tumor

Fluctuations in state of consciousness
Anisocoria
Nuchal rigidity
Imbalances of extraocular muscles
Cardiopulmonary and thermoregulatory disturbances
Pyramidal tract signs
Decerebrate rigidity

Source: From Schwartz and Rosner (1941).

A detailed clinicopathologic study of mesial temporal lobe herniations due to supratentorial tumors found that seven signs and symptoms occur regularly (Schwartz and Rosner, 1941) (see Table 25–3). The syndrome arises when an expanding supratentorial mass lesion displaces the uncus against the tentorial notch and thus compresses the ipsilateral third nerve, causing venous engorgement of the diencephalon, hippocampus, and brain stem. Consequent compression of the ipsilateral cerebral peduncle produces contralateral pyramidal tract dysfunction manifested by hemiparesis, hyperreflexia, and Babinski's sign. Infrequently, the cerebral peduncle contralateral to the mass may be caught against the tentorial notch and produce hemiparesis ipsilateral to the tumor. This is known as *Kernohan's notch phenomenon* (Kernohan and Woltman, 1929). Symptoms of herniation of the mesial temporal lobe usually progress from ipsilateral third nerve paresis, altered consciousness, and hemiparesis to vasomotor and respiratory instability over a course of hours, so prompt recognition and expedient intervention are essential if catastrophe is to be averted.

The tonsil of the cerebellum or the gyri of the flocculonodular lobe may herniate against the medulla oblongata when a mass in the posterior fossa expands. These attacks can be confused as a seizure unless a careful history is taken and neurologic examination performed. Respiratory arrest and autonomic dysfunction can rapidly ensue with little premonitory warning other than intermittent spells of the kind well

described by Jackson (1871) in a report of a patient with a midline cerebellar tumor:

> His hands were clenched; his forearms were flexed on the arms which were generally kept to the sides. The head was drawn back and the back was curved. His legs were always extended to the fullest possible degree, the feet being arched backwards. Sometimes he passed feces and urine in an attack. The seizures generally lasted three or four minutes, and, when passing off, they returned if he were moved about. He was not unconscious. . . .

A posterior fossa mass must be considered in any cancer patient who experiences vague symptoms of dizziness, tinnitus, vertigo, and blurred vision accompanied by nausea, vomiting, nuchal rigidity, or abnormal eye movements. Keen awareness of the possibility of an expanding posterior fossa lesion is critical, as surgical evacuation of a posterior fossa mass can restore normal function provided that irreversible damage to rhombencephalic structures has not occurred.

Frontal lobe masses can cause displacement of the cingulate gyrus and the anterior cerebral arteries under the falx cerebri, producing compressive ischemic injury of this important limbic system structure. Patients with subfalcine herniation demonstrate varying degrees of abulia or lack of interest in their surroundings. They become apathetic, withdraw, and have slow, minimal responses. Grasp (unilateral or bilateral) and suck reflexes may be released. Subfalcine herniation proceeds to coma at a more leisurely pace than the other herniation syndromes do and can even be compatible with long, albeit neurologically reduced, survival.

TREATMENT CONSIDERATIONS

Alterations in consciousness due to structural disease must be recognized so that treatment can be instituted promptly and irreparable damage to the brain can be avoided. Few endeavors in medicine require equal clinical tenacity. Alterations in consciousness due to structural disease often occur in patients with advanced stages of cancer, and the clinician must exercise considerable judgement when designing a treatment plan. The best plan is one that seeks to provide the highest possible quality of life for the patient while taking into account overall prognosis and the patient's wishes for aggressive or palliative therapy.

Monitoring

Except in the perioperative setting, invasive and expensive continuous intracranial pressure monitoring is not justified in the management of cerebral edema due to CNS neoplasm. Physiologic testing, including electroencephalography and the measurement of brain stem auditory and somatosensory evoked potentials, has improved the understanding of how intracranial catastrophe occurs (Stone et al., 1990, Lindsay et al., 1990). Noninvasive transcranial Doppler monitoring is an indirect measure of intracranial pressure (Trieb et al., 1998), and many invasive probes are presently used clinically to monitor intracranial pressure as well as regional oxygen saturation, jugular bulb oxygen saturation, and cerebral perfusion pressure (Nara et al., 1998). While useful for understanding the pathophysiology of increased intracranial pressure, these techniques are of limited value for oncologic patients, for whom the etiology of raised intracranial pressure is the greatest determinant of outcome. Except for patients who are paralyzed or in pharmacologically induced comas, careful and frequent neurologic examination remains the most practical and cost-effective means of examining patients with coma due to tumors.

General Measures

Pain can greatly increase intracranial pressure, and reluctance to treat pain because of concerns about confounding the neurologic examination is not only cruel but foolish, particularly as both narcotics and barbiturates lower intracranial pressure (Williams and Hanley, 1993). Muscle relaxants are widely used in intensive care units, especially to contend with patients who resist ventilatory support. These should be used only when critical to patient management and then only with assurance that the patient is adequately sedated so that he or she will not experience the horror of being paralyzed on a ventilator and in pain.

Changes in thoracic venous return during Valsalva's maneuver, coughing, positive pressure ventilation, and endotracheal suctioning can dangerously elevate intracranial pressure, but the elevation can be minimized by gently sedating the patient (Ersson et al., 1990) and using prophylactic hyperventilation. For similar reasons, neck constriction by bandages and endotracheal tube ties must be avoided. A stool softener should be given to patients who are inclined

to strain. If possible, the head should be elevated to an angle of 30 degrees, which serves to lower intracranial pressure without unduly diminishing carotid and vertebral artery pressures (North and Reilly, 1990).

Fever must be treated aggressively with antipyretics and, if ineffective, a cooling blanket. Hypotension can be disastrous in a patient with increased intracranial pressure, as it triggers autoregulatory mechanisms to induce cerebral arteriolar dilatation, promoting further elevation of intracranial pressure and potentially diminishing cerebral perfusion pressure. Free water (hypotonic fluids such as 5% dextrose in water) must be avoided, even as a vehicle for delivering medication. Hyponatremia promotes migration of free water from the intravascular space into the cerebral interstitium and must be scrupulously avoided. Furosemide and acetazolamide may be used for a short time to maintain osmolality at 300 to 310 mOsm, but the clinician should not allow hypovolemia to develop (North and Reilly, 1990). Clinicians should bear in mind a prospective study of 244 patients with subarachnoid hemorrhage that demonstrated less cerebral ischemia and improved survival for patients not treated with fluid restriction or antihypertensive therapy (Hasan et al., 1989).

Acute Increased Intracranial Pressure and Herniation

A number of methods including hyperventilation, osmotic agents, and corticosteroids can be used to reduce acute increased intracranial pressure.

Hyperventilation

Hyperventilation can lower intracranial pressure within minutes. This technique is typically utilized for operative and perioperative patients who suddenly develop increased intracranial pressure. Typically, an acutely decompensated patient is intubated and hyperventilated to a $Paco_2$ of 25 mm Hg; once the patient has responded, the $Paco_2$ should be allowed to drift gradually up to 35 mm Hg over 1 or 2 days while the patient is carefully monitored (Williams and Hanley, 1993). Protracted hyperventilation produces hypochloremia, which can be countered with KCl infusions. In at least one study of traumatic increased intracranial pressure, hyperventilation was found to diminish brain tissue oxygenation (Kiening et al., 1997), so caution must be exercised in its use.

Osmotic Diuretics

Osmotic diuretics work by establishing an osmotic gradient between the intravascular compartment and the cerebral parenchyma, promoting the movement of water out of brain tissue. Adequate urine flow is essential for osmotic diuretic therapy to succeed. One of the most popular osmotic agents is mannitol, a freely filterable isomer of the inert sugar sorbitol that is widely used to reduce intracranial pressure. Mannitol crosses the blood–brain barrier poorly, which increases its efficacy as a cerebral dehydrating drug. Unfortunately, the relative lack of a blood–brain barrier in tumor deposits causes a greater dehydration effect in the contralateral normal brain than in the lesion (Reichenthal et al., 1990).

Intravenous mannitol is available as a 10% to 25% solution and is given in a dose of approximately 1 gm/kg of body weight. The solution should be given over about 20 to 45 minutes; this time frame lessens the risk of hemolysis while establishing a swift osmotic gradient between the blood and cerebral parenchymal compartments to effect cerebral dehydration. Mannitol is generally given acutely once or twice a day. While it can be given multiple times per day for several days, chronic dosing can precipitate hypovolemia and electrolyte disturbance, while accumulation of mannitol in edematous white matter can produce a reverse osmotic gradient and exacerbation of edema (Kauffman and Cardoso, 1992). Mannitol depletes intravascular volume and produces hypernatremia, so careful attention must be paid to the patient's state of hydration and electrolyte balance. Mannitol may have additional benefits for patients with elevated intracranial pressure, such as free radical scavenging and improved blood flow dynamics (Paczynski, 1997).

For as long as 80 years, hypertonic saline solutions have been known to dehydrate the brain (Weed and McKibben, 1919), but their clinical use has only recently been championed. Solutions of between 3% and 29% saline have been used to treat refractory increased intracranial pressure both in animal experiments (Scheller et al., 1991) and in limited clinical trials (Suarez et al., 1998; Schatzmann et al., 1998). Hypertonic saline augments rather than depletes intravascular volume, which consequently supports

cerebral perfusion pressure. Hypertonic saline solution's role in increased intracranial pressure management has yet to be determined (Prough and Zornow, 1998); likely it will be an important one.

Glycerol and urea (Beks and Weeme, 1967) are orally absorbed osmotic diuretics that have been used to treat brain edema. As is the case with mannitol, rebound edema is a problem in their use unless concomitant glucocorticoids are administered. Neither glycerol nor urea is excluded from the cerebrospinal fluid, which lessens their potency as cerebral dehydrating agents. Urea's clinical utility is limited because it causes gastrointestinal upset. Glycerol's effects on brain edema are more gradual in onset and more sustained than those of mannitol (Garcia-Sola et al., 1991), but a reverse osmotic gradient may be established with chronic use (Rottenberg et al., 1977) with consequent worsening of edema formation. An oral dose of 1.5 gm/kg a day given in six divided doses (every 4 hours) significantly reduces cerebral edema (Meyer et al., 1971). We have used it in an every 4 hour schedule for 3 days followed by more chronic scheduling of every 6 to 8 hours for patients intolerant of or unwilling to take enough glucocorticoid to control their brain tumor–induced cerebral edema. Glycerol must be used cautiously by patients with diabetes mellitus.

The loop diuretics like furosemide reduce cerebral edema in experimental settings (Albright et al., 1984), but they are prone to produce hypotension and thus decrease cerebral perfusion pressure. In one study of patients with cerebral edema from tumor, furosemide produced no significant reduction in edema visible on the computerized tomography scan while mannitol did (Cascino et al., 1983). Loop diuretics contribute to the electrolyte disturbances associated with osmotic diuresis, but their effect on cerebral edema is not as great as that of the other diuretics, so their routine use is best avoided. They do have a place in reducing fluid retention in patients receiving chronic glucocorticoid therapy for brain tumor edema.

Corticosteroids and Vasogenic Edema

Corticosteroids, especially dexamethasone, have been the mainstay of treatment for brain tumor edema for more than 30 years and are one of the most effective therapies for vasogenic edema, which so frequently accompanies primary or secondary tumors or abscesses. Dexamethasone remains the favored corticosteroid for treating vasogenic cerebral edema because of its potent anti-inflammatory effects, lack of mineralocorticoid activity, and relatively low binding to plasma proteins, which allows for greater availability of the drug for the brain. Despite the efficacy and widespread use of corticosteroids, the mechanisms of their beneficial action in vasogenic cerebral edema are still not fully understood.

The clinical response to steroids varies greatly and is related to differences in tumor steroid responsiveness, tissue corticosteroid receptor concentration (Yu et al., 1981), and constitutional factors. Patients with low serum albumin and cachexia may have a greater response to corticosteroids than patients with normal levels. The optimal dose of steroid depends on the individual, but, for patients with neurologic emergencies, erring on the high side of steroid dosage seems prudent. Patients with acute increases in intracranial pressure or recent decompensation in neurologic status require a loading dose of 10 to 20 mg of dexamethasone intravenously. This can quickly be reduced to 8 to 16 mg of dexamethasone a day in two to four divided doses. Dosage must be regularly adjusted based on careful clinical observation, with occasional patients requiring much higher doses. In extreme instances, boluses of 100 mg of dexamethasone may be life saving. If given over 5 to 10 minutes, these large boluses will not produce the unpleasant perineal sensations associated with more rapid infusions.

Whereas in experimental models of cerebral vasogenic edema a significant effect of steroids was noted at 1 hour (Shapiro et al., 1990), their benefit in clinical settings may not be seen for 4 to 12 hours and may not reach maximum benefit for 72 hours. For cases of life-threatening cerebral vasogenic edema, more rapidly acting measures such as osmotic diuresis or, rarely, hyperventilation should be initiated during this period before steroids take effect.

Corticosteroid Toxicities. The systemic toxicities of corticosteroids limit their use. In a retrospective series of steroid-dependent neuro-oncology patients, corticosteroid toxicity correlated with duration of use and total dose. In addition, patients with low serum albumin levels had increased steroid toxicity. More than 50% of the patients in this study had significant steroid toxicity, and almost 20% required hospitalization to manage these complications (Weissman et

al., 1987). The less serious, although certainly annoying, side effects of corticosteroids include insomnia (which may be minimized by giving the drug in two divided doses; giving about two thirds of the dexamethasone dose in the morning and the remainder in the early afternoon to mimic the natural steroid rhythm), tremor, hiccups, systemic edema, blurred vision, and euphoria.

Unfortunately, corticosteroids also produce disabling and potentially fatal complications. They induce a catabolic state and, with chronic use, may cause muscular atrophy. Chronic use may infrequently cause a severe myopathy that some clinicians feel can be remedied by switching to nonfluorinated steroids when patients must be maintained on anti-inflammatory therapy (Dropcho and Soong, 1991). Infection with opportunistic organisms occurs during chronic steroid therapy, and *Pneumocystis carinii* pneumonia typically develops during a steroid wean (Henson et al., 1991).

Gastrointestinal bleeding and bowel perforation are particularly treacherous complications of steroid therapy, although extremely rare in brain tumor patients. Glucocorticoids may mask the symptoms of intra-abdominal catastrophe until late, so any gastrointestinal symptoms in patients on glucocorticoids must be evaluated diligently. All patients taking glucocorticoids should be placed on antiulcer therapy and a bowel regularity program. The dosage must be weaned as rapidly as clinically possible, as toxicity relates to both total dose and duration of therapy. Avascular necrosis of the femoral head may complicate steroid use.

Modifying schedules to twice daily dosing with lower doses of steroid can decrease the incidence of toxicity (Weissman et al., 1991), although the prolonged half-life of dexamethasone means that a steady state may not be achieved for days. Corticosteroids should be given with caution to patients with glaucoma, diabetes mellitus, and pre-existing tuberculosis infection. Hypothalamic-pituitary-adrenal axis suppression can arise after a few weeks of steroid treatment, so patients being weaned must be checked for addisonian symptoms and signs. Hydrocortisone replacement at 20 mg in the morning and 10 mg in the afternoon may be needed for selected patients. Patients experiencing physiologic stress who are hypothalamic-pituitary-adrenal axis suppressed should be given 100 mg of hydrocortisone parenterally every 8 hours.

Corticosteroids' anti-inflammatory effects are likely responsible for most, but not all, of their salubrious effects in treating cerebral vasogenic edema. Steroids suppress leukocyte migration and their ability to elaborate lymphokines. They inhibit production, function, and release of the leukotrienes, interleukin-1, tumor necrosis factor, interferon-α, prostaglandins, phospholipase A_2, platelet-activating factor, macrophage migration inhibition factor, and neutrophil-derived tissue plasminogen activator (Haynes, 1990). Such broad effects speak for the fundamental role for steroids in moderating inflammation.

Corticosteroids improve brain compliance (Kose et al., 1989), even in patients without vasogenic edema. Other non–anti-inflammatory benefits of steroids for patients with brain edema include restoration of noradrenaline and dopamine levels in regions adjacent to tumor (Bayens-Simmonds et al., 1989; Chang, 1989) and moderation of the effects of the capillary permeability factors expressed by tumors (Ohnishi et al., 1991).

The use of more specific anti-inflammatory drugs is on the horizon. Indomethacin, given intravenously to severe head trauma patients in bolus doses of 30 to 50 mg, lowered intracranial pressure and reduced cerebral blood flow while increasing cerebral perfusion pressure (Slavik and Rhoney, 1999) and likely produces less toxicity than corticosteroids. Drugs that block discrete inflammatory processes may be attractive in the management of tumoral edema. Two tumor necrosis factor inhibitors (Bass et al., 1996; Megyeri et al., 1999) have recently demonstrated efficacy in reducing experimental brain edema, offering hope for more specific drugs with less deleterious side effects.

Hydrocephalus

Recognition of hydrocephalus as the cause of altered neurologic function demands a high level of clinical suspicion. Progressive deficits in ambulation or level of consciousness, especially if accompanied by nausea, headache, or intrascapular pain, should alert the clinician to the possibility of acute hydrocephalus. The pace of neurologic deterioration largely determines therapeutic decisions for patients with acute hydrocephalus. Rapid progression of symptoms may occur more commonly when the brain is inflamed; and the risk of cerebral herniation is far greater when

hydrocephalus is unevenly distributed within the ventricular system (i.e., noncommunicating hydrocephalus).

Computerized tomography or MRI scanning demonstrates characteristic ballooning of the frontal and temporal horns, rostral to caudal ventricular enlargement, and a band of periventricular edema. Surgical intervention with the placement of a burr hole and ventricular drain is necessary only for the acutely hydrocephalic patient who is in severe pain and/or experiences neurologic decompensation over a short period of time. External ventricular drainage may be required but carries a risk of infection and should be used for the minimum amount of time needed. Using an electrical pump to control the rate of cerebrospinal fluid drainage may lessen the patient's discomfort and ensure that excessive drainage does not occur. Upward herniation following drainage is a risk for patients who have a posterior fossa mass (Pillay et al., 1989; Rappaport and Shalit, 1989). This life-threatening complication may be avoided by removing the infratentorial lesion before shunting.

Occasionally, surgical intervention may be postponed or avoided altogether by draining cerebrospinal fluid by serial lumbar puncture (Hasan et al., 1991), provided that the hydrocephalus is communicating. Less pressing hydrocephalus may respond to corticosteroid or acetazolamide therapy. These nonsurgical measures for hydrocephalus can postpone more definitive treatment and, in some cancer patients, can obviate surgery altogether, although the side effects of medical therapy often prove intolerable over long periods of time.

CONCLUSION

The diagnosis and management of altered mental status due to structural disease is one of the most challenging tasks in clinical oncology. The physician must intervene swiftly if disaster is to be avoided, yet must act in a manner consistent with the overall prognosis and stage of the patient's underlying condition. Reviving a comatose patient with advanced bone metastasis or pulmonary disease may result in a prolonged survival but one marked by extreme discomfort.

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