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Viral encephalitis can cause devastating neurologic injury. Little is known about cerebral hemodynamics and metabolism in this condition. We report two patients with severe encephalitis, one proven and the other suspected to be due to herpes simplex, in whom the global cerebral oxygen extraction ratio (OER) and carbon dioxide (CO_2) responsiveness was assessed. OER was low in both patients throughout the acute period. CO_2 responsiveness was present initially in both and disappeared later in the more severely affected child. These cases demonstrate that cerebral hyperemia occurs in severe viral encephalitis and that hyperventilation can effectively reduce the intracranial pressure. (Henry Ford Hosp Med J 1992;40:127-30)

Viral encephalitis is an infrequent but important cause of neurologic morbidity and mortality (1,2). Neuronal damage may be due to direct viral injury or secondary to inflammation and associated edema. Cerebral edema can cause brain injury by herniation syndromes, by elevated intracranial pressure (ICP) with consequent decreased cerebral blood flow (CBF), and by increased tissue water content which may impair oxygen diffusion from the microcirculation (3).

Specific treatment is available only for the herpes simplex virus (HSV) (4). Supportive care includes measures to reduce ICP, such as hyperventilation and osmotic diuretics (5). These interventions are undertaken ostensibly to improve cerebral perfusion pressure and therefore CBF. However, little is known about adequacy of CBF, cerebral oxygen consumption, and the cerebrovascular response to hyperventilation in severe encephalitis. We present two patients with encephalitis, one proven and the other suspected to be due to HSV, in whom the global cerebral oxygen extraction ratio (OER) was quantified and carbon dioxide (CO_2) responsiveness was tested.

Case Summaries

Patient 1

A 21-day-old (34-week gestation) girl presented with brief apneic episodes following several days of progressively decreasing alertness and poor appetite. She was born vaginally with a birthweight of 2.15 kg (4.73 lbs). The mother was a chronic drug abuser and homeless, but denied ever having symptoms of genital herpes infection.

The patient's vital signs on admission were as follows: temperature 33.5 °C (92.3 °F), heart rate 140 beats/min, respiration 20 breaths/min, and blood pressure 76/40 mm Hg. Her weight was 2.18 kg (4.79 lbs). She appeared lethargic, hypotonic, and malnourished. The fontanelle was full but not bulging. There were no skin lesions or organomegaly. The remainder of the examination was unremarkable.

Cerebrospinal fluid (CSF) results are shown in Table 1. Electroencephalography (EEG) showed diffuse slowing with periodic lateralized epileptiform discharges over the right central area. The hemogram showed a WBC count of 10,300/μL with 40% neutrophils, 32% bands, 21% lymphocytes, and 5% monocytes. Other admission studies revealed normal serum chemistries including ammonia and liver transaminases, prothrombin time, partial throboplastin time, urinalysis, and urine metabolic screen. Cranial computed tomograms are shown in Fig 1.

The patient was treated with ampicillin, gentamicin, and acyclovir (30 mg/kg/day). For seizures she received phenytoin and phenobarbital and required mechanical ventilation for frequent apnea.

Despite treatment, her level of consciousness deteriorated to the point of obtundation and her fontanelle became tense. ICP monitoring was not undertaken because of thrombocytopenia, and mannitol was administered empirically. Acyclovir was discontinued after 14 days and vidarabine (15 mg/kg/day) was used for a 10-day course. Antibiotics were stopped after five days.

Viral cultures of the stool, urine, and pharynx were negative. Repeated CSF viral, fungal, mycobacterial, and routine bacterial cultures were also negative. HSV II IgM was positive and HSV II IgG titers rose over a two-week period (Fig 2).

Ten weeks after admission, the baby was discharged to foster care in a vegetative state.

Patient 2

A 10-year-old girl presented with a three-day history of progressive lethargy and generalized headache and a brief focal seizure involving the left side of her face. Upon admission to the emergency department, she was lethargic. A second seizure began in the left side of her face, spread throughout the left side of her body, and culminated in a generalized tonic-clonic attack lasting 15 minutes. She was treated with intravenous diazepam and phenobarbital. Because of hypoventilation she was intubated.

In the intensive care unit her vital signs were as follows: temperature 37.2 °C (98.9 °F), blood pressure 120/63 mm Hg, and pulse 112 beats/min. She responded to sternal rubbing with nonpurposeful movements

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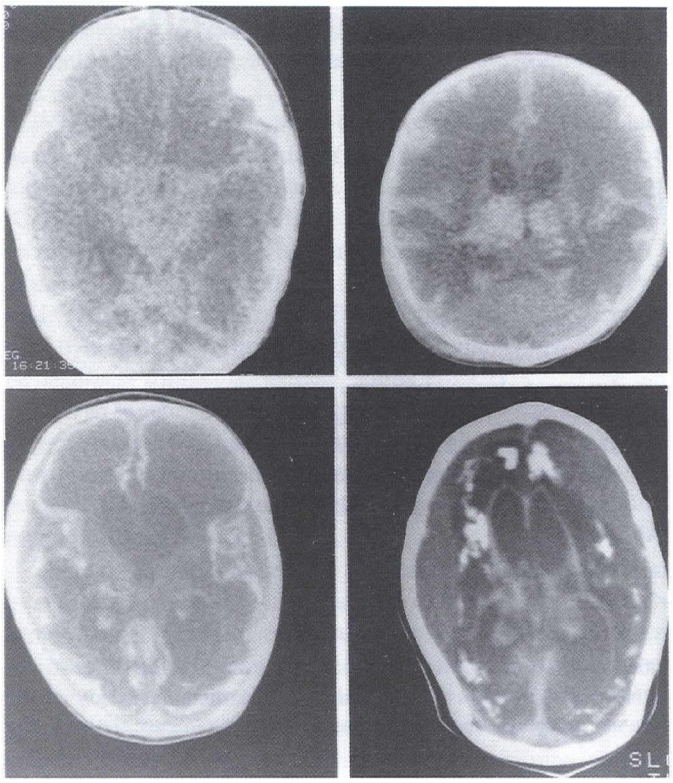

Fig 1—Computed tomography scans of patient 1. Day 2 (upper left) reveals diffuse edema. Day 12 (upper right) demonstrates less edema with reappearance of the lateral ventricles. On day 25 (lower left), generalized atrophy and early calcification appear. At three months (lower right), severe atrophy, calcification, and bilateral subdural collections are seen.

and had left hemiparesis. Brainstem reflexes were normal and the remainder of the examination was unremarkable.

Computed tomography revealed mild swelling of the right temporal lobe with displacement of the right lateral ventricle. EEG demonstrated mild diffuse slowing with focal high amplitude slow waves over the right temporal lobe. Routine CSF studies are shown in Table 1. Repeated cultures for bacteria, enteroviruses, fungi, and acid-fast bacilli were negative. CSF and serologic studies for syphilis were also negative.

She was treated with acyclovir (30 mg/kg/day) for 10 days. She was also treated with hyperventilation and mannitol as necessary to keep ICP below 20 mm Hg. On day 4, her ICP monitor and endotracheal tube were removed. She was lethargic but arousable. On day 14 she was discharged from the hospital with moderate left hemiparesis and some difficulties with speech and concentration.

Seven months later the patient had some residual left-hand clumsiness and mild difficulty with concentration and word finding, but she performed satisfactorily at school and in her usual daily activities. Repeat computed tomography was normal.

Materials and Methods

Jugular bulb catheterization was performed using the transcardiac route (6) in patient 1 and the direct jugular puncture technique (7) in patient 2. Correct placement of the catheters was confirmed radiographically. For determination of cerebral

Table 1
Cerebrospinal Fluid Values

	Patient 1			Patient 2	
Day	1	2	10	1	3
RBC/μL	50	1,202	376	1	2
WBC/μL	99	80	253	26	132
Neutrophils (%)	0	1	0	52	85
Protein (mg/dL)	219	306	660	16	21
Glucose (mg/dL)	59	54	16	121	75

OER, simultaneous sampling of arterial and jugular venous blood was performed. Arterial blood was analyzed on the ABL 3 (Radiometer, Copenhagen, Denmark), and venous oxygen saturation was directly measured on the Co-Oximeter IL 282 (Instrumentation Laboratories, Lexington, MA). Hemoglobin was quantified directly. Cerebral OER was calculated using standard formulas:

$$O_2 \text{ content} = (Hb \times 1.34 \times O_2 \text{ saturation}) + (PO_2 \times 0.003)$$

$$OER = \frac{\text{Arterial} - \text{Venous } O_2 \text{ content}}{\text{Arterial } O_2 \text{ content}}$$

CO_2 responsiveness (cerebral vasoconstriction due to hypocapnia) was tested by determining the OER at baseline ventilator settings and after 5 minutes of increased minute ventilation. An increase in OER indicates an appropriate fall in CBF due to hypocapnic cerebral vasoconstriction. Also, ICP changes were assessed during hyperventilation, grossly by fontanelle tenseness in patient 1 and more precisely in patient 2.

Patients were monitored by serial Glasgow Coma Scale assessments (8).

Results

OER data are summarized in Table 2. Hemoglobin concentration was maintained ≥ 10.0 g/dL and PaO_2 > 80 torr. Neither patient experienced hypotension. No complication from jugular bulb catheterization occurred.

Hyperventilation reduced the $PaCO_2$ by > 10 torr in all instances and increased the OER initially in both patients (Fig 3) but failed to do so later in the more severely affected girl. ICP decreased with hyperventilation, as evidenced by an obvious softening of the bulging fontanelle, only during the first five days in patient 1 but throughout the course of ICP monitoring in patient 2, with a decrease in ICP of at least 5 torr.

Discussion

Cerebral venous sampling is an increasingly common part of monitoring the brain-injured patient (7,9-12). It allows calculation of OER and CBF and the metabolism of oxygen, glucose, and lactate. This information provides feedback for the titration of brain-specific therapy as well as neurologic prognosis. Most often cerebral venous blood is obtained from the internal jugular venous bulb which provides an admixture of venous effluent

Table 2
Cerebral Oxygen Extraction Ratio and Other Data

	Patient 1			Patient 2		
Day	1	2	10	1	2	3
Coma score (best)	8	8	7	6	8	14
ICP (peak in torr)	—	—	—	20	20	8
Phenobarbital (μg/mL)	12.7	16.1	20.5	33.6	34.0	35.1
Serum pH (mean)	7.38	7.44	7.46	7.48	7.45	7.43
$PaCO_2$ (mean in torr)	36	31	30	26	23	32
OER (mean)	0.20	0.14	0.13	0.19	0.30	0.30
Measurements	2	4	4	3	4	2

with minimal extracerebral contamination (13,14). A major limitation is that only global, not regional, calculations can be made. Nonetheless, it is a more direct approach of assessing the adequacy of cerebral perfusion than is ICP monitoring. ICP monitoring provides important pressure-volume relationship data. Therefore, jugular bulb monitoring may complement the information provided by ICP monitoring.

The cerebral OER is the fraction of oxygen delivered to the brain that is taken up for metabolism. Normally the cerebral OER is approximately 0.30 during eucapnia (15). The OER increases to compensate for a decrease in oxygen delivery or an increase in oxygen consumption. However, at a certain point the brain becomes less effective in oxygen extraction, and complete compensation for declining oxygen delivery will not occur. As a result, oxygen consumption will decrease and cerebral energy stores and function will deteriorate, ultimately culminating in neuronal death. In the nonanemic patient, an OER < 0.45 is consistent with adequate oxygen delivery (16,17).

Severe viral encephalitis, especially when caused by HSV, is associated with brain swelling and increased ICP. Data on CBF, OER, and cerebrovascular CO_2 responsiveness are scant. Shapiro and Eisenberg (18) studied five adults during the acute stage of St. Louis encephalitis. Four patients were alert and cooperative and had normal CBF and a wide range of cerebral oxygen consumption. Their OER was elevated with a mean of 0.50, at least partially attributable to hypocapnia (mean $PaCO_2$ 33 torr). The single comatose patient also had a normal global CBF despite a $PaCO_2$ of 30 torr, but had markedly depressed oxygen consumption with an OER of 0.20. Paulson and associates (19) studied six adults with acute encephalitis of unknown cause; four were in comas. Both global CBF and oxygen consumption were depressed but OER was not measured. Focal hyperemia, impaired pressure autoregulation, and loss of CO_2 responsiveness were each present in some. Unfortunately, interpreting this information is difficult because these patients were studied under general anesthesia which alters cerebral metabolism and hemodynamics. More recently, Launes and associates (20) detected focal hyperemia by single photon emission computed tomography in all six adults studied with HSV encephalitis and in none of eight with non-HSV encephalitis. These reports suggest that cerebral hyperemia occurs frequently in severe viral encephalitis, especially HSV; that hypocapnia may not always induce cerebral vasoconstriction; and that cerebral oxygen consumption decreases in the comatose patient. Our study supports the first two findings. Both patients had low or normal OERs despite hypocapnia, indicating focal or generalized hyperemia. In patient 2, this condition attenuated as she improved.

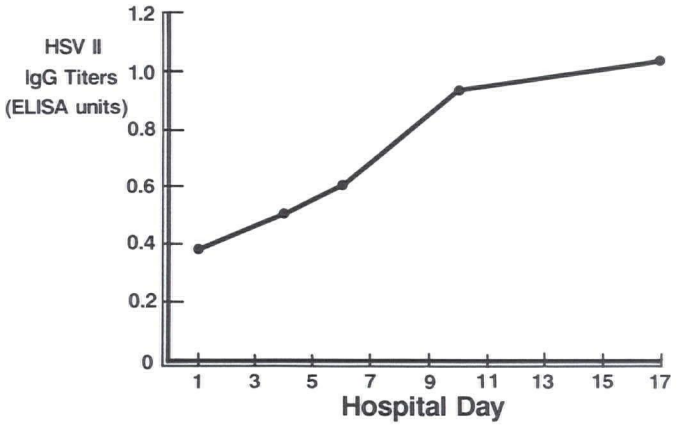

Fig 2—Serologic confirmation of HSV infection in patient 1.

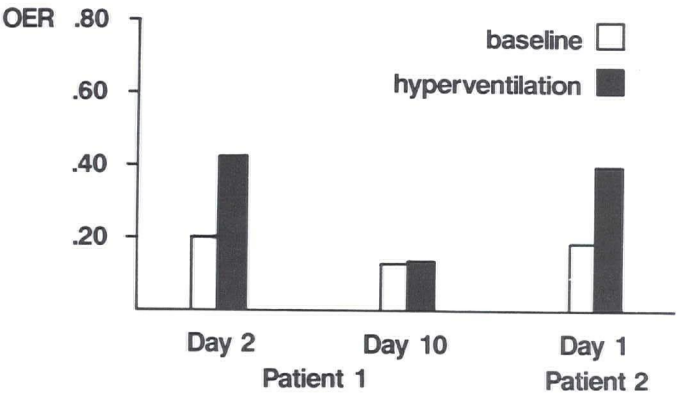

Fig 3—Impact of hyperventilation on cerebral OER.

Our findings indicate that cerebral hyperemia occurs in children with severe viral encephalitis and that hypocapnia increases cerebrovascular resistance and decreases ICP. Therefore hyperventilation can effectively treat intracranial hypertension. Whether this or any other brain-specific supportive technique improves outcome remains unknown.

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