Neurosurgical Experiences with Herpes Simplex Encephalitis*

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Neurosurgeons must differentiate herpes simplex encephalitis from other rapidly-expanding middle fossa lesions by early diagnostic procedures including brain biopsy. Successful therapy may depend upon prompt surgical decompression of the massive cerebral edema that is often found. The purpose of this paper is to record our experiences with various methods of reducing increased intracranial pressure in three consecutive cases of proven herpes simplex encephalitis during a 2-year period.

In 1941, Smith, et al.,29 demonstrated both herpes simplex virus and Cowdry type-A intranuclear inclusion bodies in the brain of a child with encephalitis. Since then, herpes simplex has been suggested as the etiologic agent in cases variously labeled as acute inclusion body encephalitis,9,9,15 acute necrotizing encephalitis,1,11 acute necrotizing hemorrhagic encephalitis,4 and even acute hemorrhagic leukoencephalitis.22

The patient with acute encephalitis due to herpes simplex virus often presents a characteristic appearance9 which begins with the abrupt onset of fever, headache, drowsiness, occasional stiff neck, and convulsions. More specific symptoms such as dysphasia, psychomotor phenomena, and olfactory hallucinations point toward the maximally affected temporal and orbital regions. Early involvement may be predominantly unilateral. Electroencephalograms, radioisotope scans, and x-ray contrast studies may all localize to one temporal lobe. Abscess or other rapidly expanding lesions of the temporal area must then be ruled out.1,4,19,22,26

Cerebrospinal fluid pressure may be elevated, and pleocytosis is usual. Viral cultures of cerebrospinal fluid, however, are rarely if ever positive.9,12 Diagnosis is usually established in retrospect by the demonstration of a greater than fourfold rise in serum antibody titer to herpes simplex virus.9,22 Early diagnosis is made from brain biopsy material by demonstrating the characteristic inflammatory changes of acute encephalitis in association with Cowdry type-A intranuclear inclusion bodies,1,12,16 or by direct isolation of herpes simplex virus from brain tissue.21,30

Herpes simplex encephalitis may vary in severity,20,28 but spontaneous recovery is extremely rare in any patient who has become comatose.25 It commonly is associated with severe neurological residue or death,9,24 which often may be secondary to cerebral edema, intracranial hypertension, and transtentorial herniations rather than to irreversible neuronal damage by the virus itself.11,22 It would seem reasonable that when increased intracranial pressure is present, its relief prior to the stage of permanent brain-stem damage might increase the chances for useful survival.1,7,14,22

Case Reports

Case 1. The patient, a 25-year-old white man, developed malaise, nausea, photophobia, and temperature elevations to 106°F. The next day he became lethargic, confused, and disoriented.

Examination. The patient was admitted to the hospital 4 days after the onset of symptoms with a temperature of 102°F and a pulse rate of 80 per minute. Somnolence and dysphasia were present, yet he could perform simple calculations. Mild right facial weakness and right-sided hyperreflexia were found. The peripheral blood white-cell count was 18,500 with 85% polymorphonuclear cells. Cerebrospinal fluid cell count was 160 with 95% lymphocytes, 40 mg% protein, 64 mg% glucose, and an opening pres
sure of 300 mm of water. There was focal
electroencephalographic slowing in the left
frontotemporal area. On the day of admission
bilateral carotid arteriograms showed a slow
circulation time but no further abnormality.

Operation. A left temporal burr hole was
made and a needle biopsy taken, which
showed extensive necrosis with perivascular
cuffing, focal polymorphonuclear and plasma
cell infiltration, vascular congestion, and
hemorrhage. Intraparenchymal inclusion bodies
were not found.

On the sixth postoperative day, bilateral
sixth nerve palsies and myoclonic movements
were noted. The patient received penicillin,
chloromycetin, streptomycin, isoniazid, am-
photericin B, and dexamethasone. However,
he became increasingly lethargic, and cere-
brospinal fluid pressures rose to 550 mm of
water over the next 10 days. Constant
ventricular drainage was established. A
ventriculogram showed dilatation of both
lateral ventricles without shift or filling
defect. Cardiac arrest occurred on two occa-
sions during anesthesia induction for the
placement of a ventriculo-peritoneal shunt.
The shunt was finally established after 35
days of external ventricular drainage. Seven
days later, the shunt required revision, and
biopsy again revealed necrotizing encephali-

tis, this time with extensive gliosis. In spite
of a functioning shunt, the patient remained
comatose until his death 16 days later.

Postmortem examination. There was ex-
tensive cystic necrosis of both temporal
lobes and mild dilatation of the ventricular
system (Fig. 1). Virus was not recovered
from cerebral tissue in this case, but a rise in
serum antibody titer to herpes simplex virus
from less than 1:4 to greater than 1:256 was
demonstrated.

Case 2. A 30-year-old white woman was
vacationing in Austria when she suffered
two generalized convulsions which were fol-
lowed by several days of headache and
lethargy. She returned to this country and
was admitted to a local hospital with mild
temperature elevation and a tendency to
“talk in a stream.” Lumbar puncture re-

ealed an opening pressure of 160 mm of
water, 50 mg% protein, 30 lymphocytes,
and negative bacterial cultures.

Examination. The patient was transferred
to the Peter Bent Brigham Hospital with a
temperature of 104°F, a pulse of 112 per
minute, a stiff neck, and bilateral Kernig’s
signs. She was disoriented, had difficulty
naming common objects or parts of her body,
and exhibited a right facial weakness and
right homonymous visual inattention. The
peripheral blood white-cell count was 8,000
with 57% lymphocytes. Electroencephalog-
raphy showed slowing over the left hemi-
sphere, echoencephalography showed devia-
tion of the midline toward the right, and
Hg203 scanning showed increased radioac-
tivity over the left temporal area (Fig. 2).
Antibiotics were started. On the second
hospital day a left carotid arteriogram
showed marked elevation of the middle

cerebral artery with minimal left-to-right
shift of midline vessels (Fig. 3). On the third

Fig. 1. Cystic necrosis of temporal lobes 2$ months
after the onset of illness. Case 2.

Fig. 2. Anterior coronal Hg203 scan. Note the increased
left temporal uptake. Case 2.
day she was more somnolent, and right hemiparesis developed.

Operation. A left temporal burr hole was made on the third day after admission and a needle biopsy taken. The brain was grossly swollen and necrotic, but not purulent. Microscopic study failed to show typical Cowdry type-A intranuclear inclusions, but severe necrotizing encephalitis was obvious. Dexamethasone was started in a dose of 16 mg every 24 hours. On the fifth day, three generalized seizures occurred followed by semicoma and intermittent decerebrate posturing. Spinal fluid at this time was xanthochromic with 80 lymphocytes and an opening pressure of 450 mm of water. Several doses of 30% urea were given intravenously over the next 48 hours, with no appreciable change.

Second operation. A left subtemporal decompression was then performed and a second biopsy taken for viral cultures. The patient continued to deteriorate and died on the ninth hospital day, approximately 19 days after the onset of illness.

Autopsy examination. The brain exhibited severe, generalized edema with necrosis of the left temporal lobe. Microscopically, both temporal lobes were the most involved by encephalitic changes. No intranuclear inclusion bodies were found. Herpes simplex virus, however, was cultured from the left temporal lobe, as it had been twice before by surgical biopsy. Cultures of all other lobes of the cerebral hemispheres and cerebellum, and of the brain stem, spinal cord, and cerebrospinal fluid were negative.

Case 3. A 34-year-old white man developed malaise and right retro-orbital headache. The following day he experienced seven episodes of dizziness, and peculiar unpleasant odors of about 2 minutes' duration.

Examination. The patient was admitted to the hospital 2 days after onset of symptoms. He had a temperature of 102°F, a pulse of 80 per minute, and a stiff neck. Mental status, including recent memory, was intact. Plantar response was equivocal bilaterally. The remainder of the neurological examination was normal. Cerebrospinal fluid pressure was 140 mm of water with 65 lymphocytes. An EEG revealed marked slowing over the right frontotemporal region with periodic high voltage discharges. A Hg\textsubscript{2} scan showed abnormal uptake over the right temporal area.

By the fourth hospital day, a left upper homonymous quadrantanopsia and left hemiparesis had developed. A right carotid arteriogram showed evidence of a temporal lobe lesion. The patient became increasingly lethargic and amnesic with inappropriate and bizarre behavior patterns.

First operation. On the fifth day a twist-drill hole was made, and a right temporal lobe biopsy showed softening but no hematoma or purulent material. Microscopically, inflammation and intranuclear inclusions

![Fig. 3. Left carotid angiograms, anteroposterior view (left) and lateral view (right), showing elevated middle cerebral artery. Case 2.](image-url)
consistent with herpes simplex encephalitis were found (Fig. 4), and viral cultures were positive for herpes simplex. The patient continued to deteriorate, developing complete left hemiplegia and left hemianesthesia. On the seventh day, the right pupil became dilated, and intermittent decerebrate postures of the left extremities occurred.

Second operation. An extensive left frontotemporo-parietal decompressive craniectomy was performed. The dura was opened widely, but no brain tissue was excised. Following surgery, 40 mg/kg per 24 hours of 5-iodo-2'-deoxyuridine (IUDR) was started by constant intravenous infusion. The dose was raised the next day to 80 mg/kg per 24 hours and continued for a total dose of 39 gm. On the day after decompression, decerebrate posturing became bilateral and both pupils were maximally dilated. The left pupil became smaller following a 90-gm intravenous infusion of 30% urea.

Third operation. A similar large decompressive craniectomy on the left side was carried out. Slow improvement began, and 5 days later, purposeful movements were possible with the left hand.

Postoperative course. Between the 17th and 25th hospital days, a transient but severe drop in peripheral blood white-cells to 1,690 and platelets to 3,500 occurred. Total bilirubin rose to 2 mg%, LDH to 490 units, and SGOT to 900 units. A gastrointestinal hemorrhage occurred, requiring 3,500 ml of whole blood in replacement. These events, although alarming, were transient and were interpreted as manifestations of IUDR toxicity. By the 22nd hospital day, the patient was able to move his arms and legs and open his eyes to verbal command. On the 44th day, there was only a mild left hemiparesis and left superior quadrantanopsia. He remembered names and did simple arithmetic problems without mistakes. His attention span was short, and he lacked spontaneity but was able to read, interpret, and retain the contents of newspaper articles. Cranioctomies were performed at 2 and 4 months postoperatively (Fig. 5). At 6 months, his mental status had seemingly returned to normal, and only the left homonymous visual field defect remained.

Discussion

Although herpes simplex encephalitis occurs in all age groups, our three patients were all young healthy adults. Each developed a febrile illness with somnolence or lethargy and a unilateral neurological deficit (Table 1). In this early phase, positive studies pointed to one temporal lobe (Figs. 2 and 3). Each patient deteriorated to coma and decerebration over the next several days.

The pathological changes of acute encephalitis were seen in each case. The end stage, gross destruction of cerebral tissue typically most severe in the temporal
regions, was found at autopsy in Case 1, 2½ months after the onset of illness (Fig. 1). Cowdry type-A intranuclear inclusions (Fig. 4) were seen only in Case 3. The etiological diagnosis was established by a significant rise in serum antibody titer in the first case and by direct isolation of the virus in the two subsequent cases.

Before diagnosis in the first two patients, multiple antibiotics were used with no discernible effects; 5-ido-2'-deoxouridine (IUDR) was used systemically in the third case. This drug is an analogue of thymidine which is effective in vitro against DNA viruses including herpes simplex.13,27 Its principal clinical application to date has been in the treatment of herpetic keratitis.17,23 The rationale for the selection of IUDR rather than immune globulin, thiosemicarbazones, or cytosine arabinoside, and the details of its use in this case, are described in a separate report.5 The concurrent use of surgical decompression and IUDR makes it difficult to assign credit for the ultimate improvement which ensued in the third case. Immediate relief from uncal herniation, however, appeared to have resulted from the large surgical decompressions.

Increased intracranial pressure, although apparently not inevitable in herpes simplex encephalitis,5 is frequently found9,12 and was noted at the time of biopsy in all of our cases. The use of dexamethasone to reduce cerebral swelling in the first two patients was unrewarding. Furthermore, there is considerable evidence that corticosteroid therapy may aggravate certain viral infections, notably varicella, herpes zoster, and herpes simplex.4,10,16,18,31 For these reasons, steroids were not used in the third case. The use of 30% urea produced a temporary reprieve but was of no lasting value in the reduction of pressure.
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In Case 1, intracranial hypertension had been documented for 16 days before ventricular drainage, and subsequent ventriculoperitoneal shunts were used. It is possible that the patient's continued deterioration and death might have been avoided by earlier and more effective relief of pressure.

Biopsy on the third day in Case 2 revealed a grossly swollen brain. This patient became decerebrate on the sixth day. Subtemporal decompression on the eighth day was of no benefit. Again, earlier and more effective relief of pressure might have produced a more favorable outcome.

In Case 3, signs of transtentorial herniation occurred 2 days after biopsy and prompted an extensive right fronto-temporo-parietal decompressive craniectomy. The patient continued to deteriorate, and the first decompression site remained tense until the following day when the left cerebral hemisphere was also widely decompressed. Gradual improvement then began, and ultimately there was an excellent recovery. Skull films (Fig. 5) following steel mesh-methylmethacrylate cranioplasties show the large size of the craniotomies.

Experience with these three cases of herpes simplex encephalitis has suggested that more extensive early surgical decompression of the brain may have a useful and perhaps life-saving effect. With the acute onset of a febrile illness where signs and symptoms suggest localization to the temporal area, herpes simplex encephalitis should be a primary consideration in the differential diagnosis. If electroencephalograms, scans, and contrast studies support the clinical localization, immediate needle exploration is recommended to rule out abscess and other temporal lobe masses. Biopsy can then be obtained for direct viral cultures and for histological study. If the diagnosis of herpes simplex encephalitis can be established, it is felt that further cautious clinical trials with IUDR are warranted.

Increased intracranial pressure may be discovered before, during, or after needle biopsy. There seems to be evidence that steroids in this situation are contraindicated. On the basis of our third case, we would suggest that extensive external decompression be carried out immediately over the most involved hemisphere. If pressure or clinical deterioration persist, decompression of the opposite hemisphere as well is recommended. Hypertonic urea or mannitol may be of great benefit at the time of these procedures. It is our feeling that ordinary subtemporal decompression is probably inadequate with this degree of cerebral swelling, just as it is in severe lead encephalopathy. Therefore, it is suggested that the largest bone flap that can reasonably be fashioned be removed and the dura opened as quickly and as widely as possible.

Summary

We have reported and discussed three cases of severe herpes simplex encephalitis. The clinical picture in each suggested a rapidly-expanding temporal lobe mass lesion. Our experience suggests that future management include:

1. Differentiation from temporal lobe abscess, hematoma, or tumor by early biopsy
2. Diagnosis by viral cultures and histological examination of brain biopsy specimen
3. Trial of an antiviral agent (IUDR) in proven cases
4. Avoidance of corticosteroid therapy
5. Early relief of increased intracranial pressure by extensive craniectomies for cerebral decompression.

References


