Acute hemorrhagic leukoencephalitis

Treatment with corticosteroids and dehydrating agents

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✔ In a case of acute hemorrhagic leukoencephalitis, proven by biopsy, a steroid preparation and dehydrating agents used in unusual amounts resulted in almost complete recovery. The characteristic features and related studies of this disease are reviewed and the policy of conservative therapy emphasized.

Acute hemorrhagic leukoencephalitis was first described by Hurst in 1941; subsequently numerous other cases have been reported. We are reporting a case successfully treated with steroids and dehydrating agents.

Case Report

A 22-year-old right-handed, white woman was admitted because of progressive right hemiparesis, confusion, speech, and emotional lability of 2 days' duration. For about 2 weeks she had had malaise, low-grade fever, nausea, and mild headache. She was 3 months pregnant and had previously been pregnant without complication.

Examination. The blood pressure was 108/64, pulse rate 74/min, respiratory rate 26/min, and temperature 100.6°F. She had no neck stiffness, tenderness, or cranial or carotid bruits. The chest was clear to auscultation, but the heart, regular of rhythm, generated a holosystolic murmur, audible over the entire precordium. The fundus of the uterus was palpable half way between the umbilicus and symphysis pubis. The patient was able to give her name, but was unable to give the date, tell where she was, or name simple objects. There was a distinct tendency to perseverate. She moved the right arm only slightly on painful stimulation. The tendon reflexes of the right arm were hyperactive while those in the legs were equal. The plantar responses were flexor bilaterally. Sensory function was difficult to evaluate due to incomplete comprehension, but it was evident that she appreciated pinprick less well over the right side. The visual fields were full, the pupils equal and reactive, and the optic discs and retinal vessels normal. She had a full range of motion of both eyes and no nystagmus, but had slight ptosis of the right eyelid. Perception of pinprick over the right side of the face was reduced, but the corneal reflexes were equal. Right facial weakness was present, most prominent in the lower part of the face. Other cranial nerve functions were normal.

Lumbar puncture revealed a pressure of 170 mm of clear colorless fluid. The protein in this fluid was 56 mg% and the cell count 30, of which 22 were polymorphonuclear cells and 8 lymphocytes. The serologic and bacteriologic studies proved negative. The hemoglobin count in the peripheral blood...
was 11.4 gm%; the hematocrit 34%; the white blood cell count 10,600, 85% of which were segmented, 2% bands, and 13% lymphocytes. The urinalysis was negative for sugar and protein, but contained 3 to 4 white blood cells per high power field. Echoencephalography showed the midline structures shifted 5 mm from left to right at the midtemporal plane. Electroencephalography was consistent with an acutely destructive, space-occupying lesion in the left parieto-occipital region.

Within 4 hours after admission the patient had become essentially mute, occasionally answering questions by saying "yes," but usually responding by shaking her head. She now exhibited profound right hemiplegia, right homonymous hemianopsia, and a Babinski sign on the right. Left carotid arteriography disclosed an ill-defined mass lesion in the left midparietal region, which was diagnosed as a hematoma (Fig. 1).

**Operation.** The left parietal region was exposed through an osteoplastic flap, tangent to the sagittal sinus. The dura was tense, and a Frazier cannula introduced through the posterior superior frontal gyrus just ahead of the central sulcus failed to encounter hematoma, abscess capsule, or perceptible altered resistance. When the dura was then opened widely along the posterior aspect of the exposure, the brain was unduly soft. A cannula introduced into the parietal lobe met so little resistance that a fluid-filled cavity was suspected but no fluid came forth when the stylet was removed. A ½ in. long cortical incision was made, and the brain was explored to a depth of 1½ in. with the aid of a small suction tip. The brain appeared extremely soft and entered the sucker tip as thick whipped cream. It appeared that a great volume of it might easily be removed by suction alone, but only enough tissue was taken for histologic examination (Fig. 2), following which the wound was closed.

**Postoperative Course.** The patient promptly regained consciousness, still with right hemiplegia and the other deficits but now accompanied by decerebrate thrusts of the right arm on painful stimuli. The pupils remained equal and reactive. She was placed on Dexamethasone, 4 mg every 6 hrs. During the first postoperative day her functions and responses changed little except that she was somewhat agitated and hyperactive. During the second day she became comatose, responding in no way except for the decerebrate reflex of the right arm on painful stimulation. Mannitol, 12.5 gm, was rapidly given intravenously, and this was followed by 40 gm of urea in 10% invert sugar over a period of 30 min. Her response to this was rather dramatic, for both pupils decreased in size and reacted better to light, the decerebrate response on the right disappeared, and she aroused enough to follow simple commands. Mannitol, 12.5 gm per 1000 cc, in 5% dextrose in water, was then begun at a rate of 80 to 100 cc per hr, while the Dexamethasone was continued as before. Later the same day, she again became unresponsive with a dilated, fixed left pupil. Again,
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40 gm of urea in 10% invert sugar was administered, and, as earlier, she responded dramatically. During the second postoperative day the white blood cell count was 20,000, 84% of which were polymorphs, 6% bands, 3% lymphocytes, 6% monocytes, and 1% eosinophils.

On the third postoperative day the patient became less responsive, had bradycardia and an enlarging, sluggish left pupil. After 40 gm of urea were rapidly given, the pupil decreased in size, remaining slightly larger than the right, however. The reaction to light became brisk, and the patient became more alert, able to say her name, and to follow simple commands. Echoencephalography on the fourth postoperative day showed a left to right shift of 8 mm. The electroencephalogram remained grossly abnormal with a constant slow wave focus in the left hemisphere, maximal in the temporal and temporo-occipital regions. The patient appeared much more alert, her vital signs remained stable within the normal ranges, and she shrugged the right shoulder on request. Dexamethasone was decreased to 0.75 mg every 6 hrs, and Mannitol in dextrose solution was slowed from 80 to 25 cc per hour. The serum electrolytes remained within normal limits during the entire period of Mannitol administration. On the sixth postoperative day the patient started on fluids by mouth, and within the next few days she began taking a full liquid diet.

Two weeks after admission, the echoencephalogram showed only a 4 to 5 mm shift of the midline structures from left to right. All parenteral medication was discontinued and oral Dexamethasone was gradually terminated. Her further hospital course was characterized by steady improvement and recovery of lost function, aided by physical and speech therapy. Before discharge, after 4 weeks in the hospital, left carotid arteriography was repeated, revealing almost complete restitution of normal appearances, for there was at this time a 2 mm shift of the midline at most, whereas initially it had been 1 cm.

At the time of discharge, the patient walked in the hospital corridors with minimal assistance. Her speech was somewhat hesitant, but she could name objects and give appropriate answers to all questions. At full term she gave birth to her second child who shows no evidence of abnormality, and the
patient herself exhibits only astereognosis and loss of position sense in the right hand, possibly related to the cerebral wound made at the time of exploration. No evidence of a visual field defect remains. The progress of the disease is chartered in Fig. 3.

**Discussion**

**Etiology**

Currently prominent among the suspected causes of acute hemorrhagic leucoencephalitis are: 1) invasion of the brain by certain bacteria or viruses; 2) effect on the brain by circulating toxins; and 3) acquired sensitivity of the brain to certain antigens. Doubt concerning viral or bacterial etiology is justified by inability, in most cases, to identify these agents. Acute hemorrhagic leucoencephalitis has occurred in association with certain viral diseases, but this occasional relationship is hardly proof of causal relationship. It has been argued that the frequent history of a premonitory upper respiratory infection in histologically proven cases of acute hemorrhagic leucoencephalitis is evidence of viral etiology, but the macroscopic and microscopic appearance of acute hemorrhagic leucoencephalitis is distinctive and unlike that of known viral encephalitis.18

Hurst’s work demonstrated that the nervous system responds to certain toxins in ways not entirely unlike those seen in acute hemorrhagic leucoencephalitis. It is reasonable to consider that some agent whose toxic properties are not yet appreciated may be the etiological factor.

**Allergy**

That acute hemorrhagic leucoencephalopathy may be a manifestation of an acquired allergic disease seems to be a possibility.49,52 The application of experimental evidence from animals14, 15, 20, 23, 26, 28, 35, 39, 40, 44, 45, 50, 52 to clinical disease calls for considerable caution, and this applies to demyelination. The component or fraction specifically responsible in the homologous and/or heterologous brain for producing experimental lesions has been shown rather conclusively to be myelin itself.46 Many other tissues have failed experimentally to produce lesions like those seen in the adult brain.23,27 Alvord46 identified an antigenic factor in the phosphatidic fraction of white matter, but could not demonstrate its presence in the cholesterol, the cerebroside, or the sphingomyelin fractions, or in the protein fraction after the extraction of all lipids. Others23 have found the protein fraction and the cerebroside sphingomyelin fractions to contain an antigenic factor.

Intracerebral injections of horse serum or egg albumin in previously sensitized animals produce lesions that are hemorrhagic, with edema, vascular thrombosis, abundant polymorphonuclear leucocytic exudate, and central necrosis. There may be merely a quantitative difference in the response between animals receiving the intracerebral injection without prior sensitization and animals with previously acquired sensitivity.4 Intracerebral injection of heterologous brain in guinea pigs and intracarotid administration of Forssman antibodies to guinea pigs also result in lesions characteristic of the Arthus phenomenon.24,50 Various enzymes in vitro, such as lipase, and those in cobra venom and clostridia Welcheii toxin, can cause demyelination,49 suggesting that non-allergic factors may also be important in demyelination.

Pathological distinctions between acute hemorrhagic leucoencephalitis and similar disease states such as brain purpura and post-infectious encephalopathy, are more certain than the distinction that acute hemorrhagic leucoencephalitis is one of the auto-immune diseases. Adams and Kubik2 distinguished four groups of demyelinating diseases: 1) multiple sclerosis, 2) acute disseminated encephalomyelitis as seen with measles and other infections, 3) cerebral sclerosis of the demyelinating type such as Schilder’s disease, and 4) acute and subacute necrotizing hemorrhagic encephalomyelopathy. Hurst’s acute hemorrhagic leucoencephalitis is in the latter category.

**Pathology**

Grossly, the brain is congested and swollen with one hemisphere being involved to a greater degree than the other. Petechial hemorrhages in the centrum semiovale spare the frontal, occipital, and temporal poles. The petechial hemorrhages may become confluent, resulting in hemorrhagic areas of variable size. The cortex and basal ganglia may be spared while the corpus callosum, brain stem, and cerebellum have microscopic

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Histologically, five characteristic lesions may be found: 1) necrosis of vessel walls, more often veins, with deposition of fibrin within the wall or in the perivascular space, 2) perivascular edema, 3) polymorphonuclear and mononuclear exudates, 4) zones of perivascular demyelination, and 5) ring and ball hemorrhages, frequently with thrombosed capillaries in the centers. Electron microscopy elucidates some of these changes. Luse and McDougall, using rabbits that had received brain emulsion and Freund's adjuvant, noted as the first change a swelling of the mitochondria in the oligodendrocytes followed by axonal denuding of myelin, which become sequestered in gitter cells. Oligodendroglia functions in the transportation of nutrients, and formation and maintenance of the myelin sheath. These cells make numerous perivascular contacts, and by reason of this position might conceivably be the first to be affected by circulating toxins, or the first to be affected by antigen-antibody reactions.

Clinical Course

The three-phase clinical picture of acute hemorrhagic leucoencephalitis is character-
istic. The prodromal period averages 5 days and may simulate an upper respiratory infection such as mild coryza with sore throat, hoarseness, and cough. Even bronchopneumonia may occur. The second or interval phase, lasting 1 to 7 days, may be unnoticed or perhaps absent, but characteristically the patient recovers completely from the prodromal phase, and returns to normal activities. The tertiary phase is heralded by the acute onset of variable neurological symptoms and signs such as headache, nausea, vomiting, fever, stiff neck, malaise, confusion, hemiparesis, hemiplegia, or even quadriplegia. Other physical findings encountered are cranial nerve palsies, variable sensory abnormalities, convulsions, and urinary incontinence. Most cases deteriorate progressively as the level of consciousness diminishes to coma and finally death.

**Treatment**

The most striking deficit in the related literature is in the lack of information about treatment. Steroids have been used to lessen brain swelling and for their anti-inflammatory effects. Surgical decompression and excision of affected brain, alone or in combination with steroids, have been instituted with survival or prolongation of life. Our case suggests that tenacious conservatism may be rewarded in the treatment of acute hemorrhagic leukoencephalitis. It seemed doubtful from the clinical deficits and the appearance of the white matter visualized during surgical exploration that the involved brain could recover, but it proved itself capable of just such a recovery. There was a point in the course of our patient (second postoperative day) when we considered an excisional or decompressive procedure, and might have proceeded had the area of involvement not been the central region of the dominant hemisphere. We now feel that surgical excision of the affected dominant hemisphere tissue is highly undesirable if any other form of treatment can hold the fatal swelling in check. If the extent of the pathologic process is great enough, the swelling and resultant pressure may be more than can be controlled by steroids and dehydrating agents, and excision or decompression may become necessary. We make the plea, however, that it be employed only after an adequate medical trial. As was demonstrated in our case, the gravity of the clinical course is almost entirely related to increased intracranial pressure, and although the disorder is short-lived, the need for prompt counteraction is great. The initial use of steroids and dehydrating agents in sufficient dosages and for an adequate period followed, if necessary, by a large external surgical decompression seems to be the logical therapeutic regime in the treatment of acute hemorrhagic leukoencephalitis. Initial internal decompression and removal of the diseased brain seem contraindicated.

**References**

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