Acute Hemorrhagic Leukoencephalitis
A Clinical and Electron-Microscopic Report of 2 Patients Treated with Surgical Decompression

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Acute hemorrhagic leukoencephalitis has been regarded as a rare and uniformly fatal neurological catastrophe. Classically, the lesions are confined to cerebral white matter, frequently unilateral but occasionally involving both hemispheres, the brain stem or even the cerebellum. From the time of the original report of Hurst\(^5\) in 1941 until that of Kristiansen et al.\(^7\) in 1956 no cases were diagnosed prior to postmortem examination. In the latter report\(^7\) of 5 surgically explored patients, biopsies of the brain in the 2 who survived were compatible with this diagnosis although histologic sections were not shown. Nevertheless, it was emphasized that all cases of acute hemorrhagic leukoencephalitis need not necessarily terminate fatally, even though the specific diagnosis had until then not been made prior to death.

It is our purpose to report 2 additional cases of acute hemorrhagic leukoencephalitis, treated promptly by internal and external surgical decompression. In the second case the brain was processed for electron as well as light microscopy.

Case Presentations

Case 1. R.C., a 21-year-old white man, was admitted to the Neurology Service of St. Louis City Hospital at 11:00 p.m. on Oct. 6, 1960 with the chief complaints of severe headache of 36 hours' duration and increasing paralysis of the left side beginning 24 hours before admission. A review of his past history disclosed an episode of "flu" in February, 1960, during which he complained of frontal headache, malaise, cough and vomiting lasting for 1 week. Two months before admission he was treated at another hospital for bilateral otitis media. He was well again until 2 weeks before his present illness, when he had a productive cough followed 1 week later by chills and vomiting. One day before admission he complained of mild headache, left-sided pain in the chest, coughing, vomiting and slight left-sided weakness. On the morning of Oct. 6, 1960, he was awakened at 6:45 a.m. by a severe right-sided headache localized mainly to the retro-orbital and temporal areas. He went to work and remained there although the left-sided weakness, headache, nausea and vomiting became increasingly worse. He noticed "tingling" and "numbness" of the left side as well as slurred speech. He returned home at 5:30 p.m. but became weaker and less alert during the evening. Later that evening his physician sent him to the hospital.

Examination. He was a thin, uncooperative, obtunded man with normal vital signs. There was partial paralysis of the right 3rd nerve, left central facial weakness and a left hemiplegia. The optic disc margins were sharp but the veins were engorged. At lumbar puncture the pressure was 170 mm. of water and the fluid was clear with only 1 white blood cell. Cerebrospinal fluid protein was 74 mg. per cent, sugar 62 mg. per cent, and chloride 115 mEq. The count of white blood cells was 19,400, hemoglobin was 14.3 gm. and urinalysis gave normal findings.

Course. Within 2 hours he became even less responsive with a dilated, fixed right pupil. Suspecting an expanding mass in the right hemisphere, a right carotid arteriogram was done which showed marked displacement of the right anterior cerebral artery to the left. The lateral projections were of no help. He was transferred immediately to Barnes Hospital by which time he was barely responsive to loud commands. The pupils were divergent with complete paralysis of the right 3rd nerve and extremely engorged retinal veins. Ventriculography was performed immediately and demonstrated a pronounced shift of the entire right ventricle to the left side (Fig. 1). During this procedure he had a generalized seizure.

Operation. As there was no definite anterior-
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posterior limit to the process, a large right frontoparietotemporal bone flap was reflected. The dura mater was extremely tense. The brain was needled in all directions in search of an abscess, hematoma, or cystic fluid, but only mushy white matter could be aspirated. Thirty per cent urea was given intravenously prior to opening the dura mater more widely but little relaxation was obtained. The meninges appeared slightly cloudy. The subcortical white matter in the frontal lobe was entered and found to be soft, edematous, and easily aspirated. A large amount was removed in search of a possible small tumor, but none was found. Though the brain swelling had been reduced it was still necessary to make a large temporal bone decompression in order to replace the bone flap.

Pathologic Report. The surgically excised cerebral tissue was fixed in formalin, embedded in paraffin, and stained with hematoxylin and eosin, phosphotungstic acid-hematoxylin and by Weil's myelin stain. There was a distinct polymorphonuclear exudate present in the subarachnoid space, and about many of the larger intracerebral blood vessels. The cerebral cortex was normal except for the perivascular cellular infiltrate. In contrast to the cortex there was a distinct increased cellularity in the underlying white matter (Fig. 2). Numerous recent ball- or ring-hemorrhages (Fig. 3) were present, often around a central small blood vessel. Neutrophiles ringed some vessels. There was perivascular demyelination, especially in the regions of hemorrhage. Gitter cells were numerous. Edema was prominent.

Postoperative Course. He remained semicomatose for several days and a tracheostomy was necessary. Improvement was gradual and after 10 days he was able to talk rationally but still was severely hemiparetic on the left side. After several weeks of intensive physical rehabilitation he was able to walk and improved enough to go home, although weakness of the left arm and partial paralysis of the right 3rd nerve remained. A right carotid arteriogram performed 3 weeks after operation was considered normal (Fig. 4).

Subsequent Course. After discharge from the hospital he had several generalized seizures but since then has been seizure-free on Dilantin and phenobarbital. The neurological deficits have improved but he continues to have definite weakness of the left arm and hand, and a left homonymous hemianopsia. Function of the 3rd nerve is now normal. Extensive psychometric evaluation has shown remarkably little intellectual impairment. However, he has required psychiatric therapy because of periods of depression and anxiety but these, in large part, are caused by distressing and complicated family problems.

Case 2. C.R., a 12-year-old white girl, was admitted to St. Louis Children's Hospital on Nov. 20, 1961 with a history of convulsions and coma of 12 hours' duration. Although there was no definite history of an upper respiratory infection she had not felt entirely well for a week before admission. Two days before admission she remained in bed, slept most of the day, and the next day seemed subdued. At 3:00 a.m. on the day of admission she awakened her mother by crying out and complained of headache and abdominal pain. At 7:00 a.m. she was found on the floor convulsing. Thereafter she had numerous seizures, beginning on the left side and then becoming generalized. Between seizures she was semiresponsive and paralyzed on the left. At noon, she was treated with phenobarbital and then transferred by ambulance to this hospital, during which time the convulsions gradually subsided.

Examination. She was semistuporous and only
FIG. 2. Case 1. Photomicrograph of brain biopsy. At the left is normal cortex. At the right is cellular white matter (WM). Gitter cells are prominent. Several small areas of hemorrhage are present. 220X, hematoxylin and eosin.

FIG. 3. Case 1. This is another region in the white matter. At the right is a recent ball-hemorrhage and at the left a small vessel with perivascular inflammatory cells and foci of hemorrhage. There is also evidence of edema. 220X.
occasionally responded to loud commands. There was a profound left hemiparesis, more marked in the face and arm. Left homonymous hemianopsia was evident to gross testing. There was bilateral papilledema with hemorrhages. The deep tendon reflexes were hypoactive on the left and a left Babinski's sign was present. Her temperature was 38.8°C., pulse rate 92, hemoglobin 14.4 gm., count of white blood cells was 27,717 with 92 per cent polymorphonuclear leukocytes. Urinalysis showed + albumin, and was negative for porphyrins.

A right cerebral abscess was suspected, and carotid arteriography showed evidence of a mass lesion in the right posterior temporoparietal region (Figs. 5 and 6).

Operation. A craniotomy was performed at once. The dura mater was taut and a cannula passed into the brain encountered only firm subcortical tissue. Intravenous urea effected slight relaxation. The dura mater was opened widely and the zones of firm resistance were explored, but only edematous, rather tough white matter was found. A large amount of this tissue was removed until the trigone of the ventricle was exposed. In addition, the right temporal lobe was removed until the incisura was seen. In spite of these measures the brain continued to herniate through the dural opening necessitating a large subtemporal bone decompression before the flap could be replaced.

Pathologic Report. Multiple blocks of the tissue removed surgically were fixed in formalin and embedded in paraffin for light microscopy. Other blocks were post-osmicated in Dalton’s fluid and embedded in Epon for electron microscopy. Tissue embedded in paraffin was stained with hematoxylin and eosin, phosphotungstic acid-hematoxylin, and by Weil’s technic for myelin. Frozen sections were stained with oil-red O. There was no cellular infiltration in the meninges. The cerebral cortex appeared thinned and strikingly less cellular than the underlying white matter. Satellitosis of cortical neurons was scant. Only rarely was a cortical blood vessel surrounded by a zone of recent hemorrhage, and the relatively acellular cortex contrasted sharply with the unusually cellular white matter. The phosphotungstic acid-hematoxylin stain revealed numerous reactive astrocytes in the white matter. Perivascular areas were delineated sharply because of the even greater cellularity about them. Edema of the white matter, although marked, was focal. It was evidenced by the classic sponge-like vacuolization of white matter (Fig. 7).

The most pronounced pathologic change was the focal perivascular ball-hemorrhages (Figs. 8 and 9), scattered diffusely throughout the white matter and usually surrounding a small blood vessel—either a capillary or venule. The hemorrhages were recent but, in some, blood-cell destruction was beginning. Other vessels were ensheathed by a fibrin-like layer and external to that by a zone of red cells (Fig. 10). Rarely a small blood vessel was occluded by similar acellular eosinophilic material.

Electron microscopy revealed focal extravasations of red blood cells. The usually narrow perivascular Virchow-Robin spaces were often were dilated and packed with lymphocytes. In many areas there was a striking proliferation of fibrous astrocytic glia, the processes of which were crowded with delicate fibrils and often closely invested myelinated fibers. In these areas there were scattered lymphocytes (Fig. 11) and numerous gitter cells that contained phagocytic myelin debris (Fig. 12).

It was impossible to verify the origin of the phagocytic cells and actually some of them appeared to be of astrocytic origin. Most striking, however

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**Fig. 4. Case 1. Anteroposterior projection. Right carotid arteriogram performed 3 weeks postoperatively.**

**Fig. 5. Case 2. Right carotid arteriogram showing upward displacement of posterior portion of middle cerebral circulation.**
Fig. 6. Case 2. Arterial (left) and venous (right) phases of right carotid angiogram showing displacement of both systems to left. Greater displacement of internal cerebral vein correlates with localization on lateral projection.

Fig. 7 and 8. Case 2. (Left) The diffuse spongy character of the white matter in the zones of edema is evident. X280, hematoxylin and eosin. (Right) The ball- and ring-hemorrhages in the white matter are closely aggregated. A small vessel can be seen at the center of the upper hemorrhage. X110, hematoxylin and eosin.
was the presence of demyelinated axons. Scattered amidst normal myelinated axons were masses of myelin debris, gitter cells, fibrous astrocytic processes and distinct large axons with either no myelin sheath or only a remnant (Fig. 13). In other foci demyelinization was less prominent than edema, as demonstrated by massive dilation of glial processes with compression of adjacent myelinated fibers. Normal human white matter (Fig. 14), in contrast to either acute hemorrhagic leukoencephalitis or to experimental allergic encephalomyelitis, contains no unmyelinated axons and no evident extracellular space.

Postoperative Course. The patient’s immediate course was one of steady improvement. The day following operation she was more alert, responded verbally, but moved her left side poorly. Three days after operation diabetes insipidus developed and she was treated with Pitressin for 1 week. An electroencephalogram, done 2 weeks after operation, showed right-sided slow waves and possible left suppression. Initially, the subtemporal decompression was full but during the next 3 weeks gradually became softer. There was steady improvement in the left hemiparesis with residual impairment of cortical sensibility in the left arm and hand. One month after discharge the decompression was flat, pulsating, and only slight hemiparesis and left homonymous hemianopsia remained. The use of steroids was considered initially but in view of the relatively rapid improvement and the absence of definite therapeutic indications, none was given.

For the next 2 months she continued to improve, returned to school where she maintained a high level of academic performance. However she frequently complained of a “bad taste in her mouth,” abdominal discomfort, and occasional matutinal vomiting.

One month before her second admission she was noted to be more clumsy when walking, less dextrous with her left arm and leg, and to have gross horizontal nystagmus. Dilantin was discontinued gradually and phenobarbital dosage was lessened.

2nd Admission, April 12, 1962. She had had onset of unilateral and generalized seizures earlier the same day, some beginning on the left, others on the right. These subsided after intramuscular sodium phenobarbital.

Examination. Positive findings were a firm, protruding right subtemporal decompression, profound left hemiparesis, left hemianopsia, slurred speech, and nystagmus in all directions of gaze. Her initial state of lethargy and confusion improved to one of normal alertness by the next day. Laboratory findings on admission including count of blood cells, urinalysis, and spinal-fluid examination were within normal limits.

Course. Little improvement occurred after the 1st week of stay in the hospital. Visual acuity was markedly diminished in the left eye associated with marked pallor of optic discs. Severe paresis
FIG. 11 (upper). Case 2. Electron micrograph of white matter. A single lymphocyte dominates the field. Interspersed between normal myelinated axons is a mass of degenerating myelin (M). At the lower right is a process of a fibrous astrocyte. X8,000.

FIG. 12 (lower). Case 2. Electron micrograph of a gitter cell. The nucleus is indented by a "myelin figure" formed of the degenerating myelin lipids. Other masses of phagocytosed myelin lipids distend the cytoplasm. Adjacent myelinated axons appear normal. X8,000.
of the left face, arm, and leg remained, associated with marked loss of senses of touch and position, and stereognosis on the left.

Further laboratory investigations proved fruitless, including multiple studies for LE cells, determinations of serum arsenic and lead, urinary porphyrins, and electrophoresis of serum protein. Electroencephalograms showed marked bifrontal and right-sided slow dysrhythmia.

At this time, April 25, 1962, dexamethasone therapy was begun in the hope that further progression of her disease might be arrested. She was discharged home 1 month later on this medication as well as Dilantin and phenobarbital.

3rd Admission. Two weeks later, on June 4, 1962, she was admitted again because of severe headaches, and marked bulging of the subtemporal decompression for the previous 48 hours. During the 2 weeks at home she had fallen several times and had had one generalized seizure.

Examination. All previously mentioned neurological findings were associated with progressive bulbar involvement as evidenced by paralysis of the left 6th nerve, left palatal weakness, and a
nasal voice. On June 6, 1962 ventriculography showed marked displacement of ventricular system to the left and absence of air in the right temporal horn.

2nd Operation. Exploration through the old temporoparietal craniotomy disclosed a swollen, softened brain, as well as gliosis from the first procedure. Portions of the temporal lobe were removed for decompression and microscopic study. Administration of intravenous urea was quite effective in reducing cerebral herniation.

Pathologic Report. Histological study of the biopsy specimens showed the features of acute hemorrhagic leukoencephalitis already described. In addition areas of degeneration and gliosis were noted undoubtedly caused by the previous acute episode and subsequent operation.

Postoperative Course. She was drowsy for several days but completely oriented. Improvement was slow, associated with marked bulging of the site of decompression and severe headache. Steroid therapy was discontinued and the patient was started on Benadryl 75 mg./day. During the next 3 weeks the subtemporal decompression softened though her neurological status changed but little. At the time of discharge she was, if anything, slightly worse in all respects.

The patient never again was examined here, but letters from her family physician indicated progressive neurological deterioration—particularly of brain-stem centers, necessitating nasogastric intubation and endotracheal aspiration. The patient died on Nov. 3, 1962. Unfortunately, it was impossible to obtain an autopsy.

Discussion

It is not our intention to present in detail the clinical symptomatology of acute hemorrhagic leukoencephalitis since the recent reviews of the literature by Lander and Kulick have summarized the clinical and

Fig. 14. Electron micrograph of normal human white matter. In contrast to Figs. 13 and 15, all axons are surrounded by a thick myelin sheath. In addition, in the normal white matter no extracellular space is evident, glial processes filling the regions between the axons. X 14,000.
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pathological features as well as the theories of pathogenesis of this disease. Characteristically, most patients are young adults in good health except for a prodromal period of upper respiratory infection lasting from one day to several weeks. Neurological symptoms then appear abruptly, frequently beginning with severe headache, stiff neck, nausea, vomiting and confusion, soon followed by severe asymmetrical, or occasionally symmetrical, neurological signs. These may consist of unilateral seizures, hemi- or quadriplegia, aphasia, coma or decerebrate rigidity proceeding to death within a few days. Cranial-nerve palsies and papilledema have been noted.

Laboratory tests have been of little help in arriving at a specific diagnosis prior to histological examination of cerebral tissue. Peripheral blood studies more often than not show a leukocytosis, sometimes as high as 30,000 cells per c.mm. with marked polymorphonuclear predominance. Sedimentation rates, when reported, have always been elevated. Albuminuria is usual. Cerebrospinal-fluid pressure usually is elevated even though in some patients with advanced neurological changes it has been normal. The count of cells in the cerebrospinal fluid may vary from zero to 2800 cells per c.mm. Reports of counts higher than this have been complicated by the presence of positive bacterial cultures from the spinal fluid. Determinations of protein are of little help since they may range from normal values to 620 mg. per cent. The content of sugar has always been within normal limits.

At the time of Lander's and Kulick's reviews, only 34 cases meeting the proper pathological criteria for acute hemorrhagic leukoencephalitis could be found in the literature. Since then several additional cases have been reported. Kulick indicated that all patients died in coma, overlooking 2 survivors of 5 patients operated upon by Kristiansen. Brain biopsies were obtained from these patients at the time of craniotomy but no information was given about the gross appearance of the brain or the surgical measures undertaken. One survivor made an excellent recovery but the other continued to deteriorate.

Fig. 15. Electron micrograph of a demyelinated axon in a white tract in the spinal cord of a rabbit with experimental allergic encephalitis. X14,000.
Le Beau et al.\textsuperscript{16} also operated upon 6 of 12 patients with various forms of acute encephalitis though their only patient with histologically typical acute hemorrhagic leukoencephalitis was not treated surgically. However, in 6 others who had radiologic evidence of displacement of one lobe or hemisphere, surgical removal of large portions of involved brain was performed on the assumption that one of the more common surgical disorders was present. Since all of their surgically treated patients with these other forms of acute encephalitis died in spite of decompression, it was their opinion that nonsurgical treatment for the whole group would have been preferable had there been a reliable way to make the diagnosis beforehand. More recently, Bennett et al.\textsuperscript{2} reported 3 autopsied cases of acute necrotizing encephalitis, a disease thought to be of viral origin, in which acute mass lesions of the temporal lobe were suspected. Although surgical treatment was of no avail in 1 of these, the possible value of decompression in preventing irreversible damage from cerebral edema was realized, a suggestion supported in part by our small experience.

Patients with bilateral cerebral or brainstem involvement obviously will not present the same clinical findings and thus consideration of a hemispheric mass lesion would be unlikely. Should the diagnosis of acute hemorrhagic leukoencephalitis be suspected in such cases it is not suggested that surgical treatment be considered. Furthermore, it is recognized that advanced stages of neurological decompensation may be reached beyond which no form of therapy would be of benefit. It also seems reasonable that some patients with signs of acute cerebral disease of lesser severity and who survive their illness with or without neurological sequelae, may have had acute hemorrhagic leukoencephalitis though pathological proof would be lacking. However, until a reliable and specific laboratory test is devised, the validity of this assumption will remain in question.

Electron microscopy of brain tissue removed from our second case adds confirming evidence to the arguments of Hurst,\textsuperscript{6} Russell,\textsuperscript{13} Rankin and Dance,\textsuperscript{12} and Wolf et al.\textsuperscript{16} concerning the etiology of acute hemorrhagic leukoencephalitis. These authors, among others, have contended that acute hemorrhagic leukoencephalitis, acute disseminated encephalomyelitis and allergic encephalomyelitis are but related forms of the same fundamental process. Not only does this theory seem reasonable to us, but electron microscopy reveals that the ultrastructural changes are basically the same as those in experimental allergic encephalomyelitis. Luse and McDougall\textsuperscript{11} demonstrated that in experimental allergic encephalomyelitis the myelin sheath was destroyed and the denuded axon remained intact as can be seen in Fig. 15. Such is the case in acute hemorrhagic leukoencephalitis. In addition to demyelination with preservation of the axon there was edema, gliosis and phagocytosis of myelin debris by gitter cells.

In view of the possible role of hypersensitivity in this disease, the therapeutic use of adrenal corticosteroids or ACTH\textsuperscript{9} has been suggested but no patients thus far have been so treated. Their use was considered in our second case after the initial episode, but in view of rapid clinical improvement none was given. However, during the second admission, some 4 months later, dexamethasone was started though the effect was indefinite and disappointing. Her condition remained stable for several weeks only to become acutely worse about 6 weeks later. Brain biopsy again showed the characteristic changes of acute hemorrhagic leukoencephalitis. Antihistaminic therapy was tried next and continued until the time of death.

The part played by the use of intravenous urea in our cases during the acute illness remains uncertain. Cerebral swelling was visibly reduced but not to a degree sufficient to preclude a generous internal and external decompression to achieve surgical closure. It is our impression that all of these measures were additive in their beneficial effect, and that without them both patients might well have deteriorated to death during the early days of the illness.
Summary

Two cases of acute hemorrhagic leukoencephalitis are reported following surgical decompression.

One patient has continued to do well following the initial and only episode 2½ years ago.

The second patient, though greatly improved for 3 to 4 months, experienced progressive episodic disintegration refractory to both steroid and antihistaminic therapy. In both, the presenting symptoms and roentgen-ray studies suggested a rapidly expanding mass lesion of the right hemisphere. The severity of cerebral swelling disclosed at operation necessitated wide internal and external decompression together with intravenous urea. Light microscopic examination of cerebral tissue showed the classical findings of acute hemorrhagic leukoencephalitis, namely ball-hemorrhages, increased cellularity and edema of the white matter with sparing of the cortex. Electron-microscopic examination of tissue from one case lends support to the argument that acute hemorrhagic leukoencephalitis and allergic encephalomyelitis are related processes.

Discussion

Dr. Charles F. Barlow: I am really grateful to the authors of this paper for bringing to my attention the fact that acute hemorrhagic encephalitis (a diagnosis usually made at autopsy) can be diagnosed during life. In this case, the biopsy diagnosis was also, in part, therapeutic, which makes for an even more satisfactory situation.

I certainly agree with them that this entity is, in many respects, similar to experimental allergic encephalomyelitis in some animals, in which hemorrhage is seen occasionally. Furthermore, experimental allergic encephalomyelitis in the monkey tends to have focal intensity. I studied the permeability of the brain to trypan blue in this experimental disorder some years ago. This technique essentially tests permeability of the barrier to protein. My findings, largely confirmed by Olejewski using T1 albumin, were simply that the lesions which extended from vessels to involve brain parenchyma were abnormally permeable to trypan blue. This meant that most of the lesions in the monkey were clearly blue stained.

It would seem to me that the use of both surgical and medical decompression has good physiological basis in this situation. Urea, which we have found to require 6 hours to equilibrate with cortex, and 12 hours to equilibrate with white matter, would be expected to exert its most profound and sustained effect on the more normal brain tissue. The areas of abnormal permeability should not be as sensitive to the osmotic gradient. And, if they are extensive and focal, as was true in this case, a more direct surgical approach would seem to be indicated.

Relative to the use of ACTH or cortisone, it can be said that the effect of these agents is definite only in those animals with experimental allergic encephalomyelitis in which treatment is begun before the disease is manifest clinically.

Finally, I would like to ask if cultures and virus studies were performed on the brain tissue removed.

I would like to thank the program committee for inviting me here to discuss this interesting paper, and to see the electron-microscopic pictures, a technique which is certainly giving a new dimension to neuropathology.

Dr. Russell Myers: Just one sentence by way of admonition. The question as to the allergic versus inflammatory, possibly viral origin of the pathological changes we have seen so beautifully exhibited in the paper of Doctors Coxe and Luse should give us some pause with regard to interpretation as to etiology.

This is an admonition which I am sure has been expressed to us in many ways by our teachers and contemporaries: that the nervous system has a relatively few number of ways of responding to insult; and that the pathological changes can, at best, proffer some suggestions as to etiology, but in no way commit us to a monolithic interpretation of the etiology.

Dr. William S. Coxe: I wish to thank Dr. Barlow and Dr. Meyers for their comments. With regard to making cultures and other studies on this tissue, it might not be obvious from the paper but we were totally ignorant of what was going on at the time the patients were operated upon and did not have the foresight to submit this tissue to any other study. As a matter of fact, the first case was undiagnosed until the second one came along. Then we re-examined it.

I would certainly agree with what you said, Dr. Meyers, that the resemblance to experimentally induced lesions certainly in no way confirms the etiology of this condition.

References


