Acute Hemorrhagic Leukoencephalopathy

A Clinical, Pathological, and Radiological Correlation

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SUMMARY: Two patients with acute hemorrhagic leukoencephalopathy, one of which was pathologically proven, were serially studied with CT scanning. Both patients showed marked distinctive low density white matter changes throughout both hemispheres, which correlated with clinically involved areas. One patient recovered from the disease, perhaps due to steroid treatment, and showed slow but complete resolution of CT scan changes. We feel that CT scan findings significantly help in the diagnosis of this disease, which may be amenable to early treatment with steroids.

RÉSUMÉ: Nous avons étudié à la tomodensitométrie sériée deux patients souffrant de leucoencéphalopathie hémorragique aigue, dont un prouvé pathologiquement. Chez les deux patients on a trouvé des aires précises de basse densité dans la matière blanche des deux hémisphères; ces zones correspondaient aux aires cliniquement impliquées. Un patient a guéri, peut-être à cause d'un traitement aux stéroïdes, et a montré une résolution lente mais complète des changements en tomodensitométrie. Nous croyons donc que la tomodensitométrie peut être utile dans le diagnostic de cette maladie qui peut parfois être traitée par des stéroïdes.

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Acute hemorrhagic leukoencephalopathy (AHL), is a rare, frequently fatal disease of cerebral white matter (Hurst, 1941; Adams et al, 1949; Behan 1973). It is seen in both children and adults and both sexes are equally affected. A viral illness usually preceeds the development of this disease by several days to weeks, though many other types of predisposing conditions, such as pneumonia, vaccination or surgery, have been described (Byers, 1975).

AHL presents as a vague illness characterized by malaise, fever, and headaches, then rapidly progresses to produce focal signs of CNS disease. Hemiparesis, dysphasia, sensory loss and seizures are common. Confusion and decline in the level of consciousness to coma invariably occur (Gosztonyi, 1978). Laboratory investigations show the peripheral white blood counts to be elevated (12,000-20,000 per cu mm) with polymorphonuclear predominance. Cerebrospinal fluid (CSF) analysis typically shows a slight increase in pressure, a moderate increase in protein with levels of up to 1000 mg% being reported occasionally (Byers, 1975), and a pleocytosis of 10-1000 cells per cu mm. Initially, polymorphonuclears predominate, but a change to lymphocytosis is seen within a few days. The glucose is normal, which helps to differentiate this condition from bacterial meningitis. Red blood cells are not commonly seen in the CSF (Behan, 1973).

The electroencephalogram shows diffuse slow wave activity. Radioisotope brain scan is normal; angiography may suggest a space occupying lesion or minor abnormalities or it may be normal (Pexman et al 1974).

Although spontaneous recovery has been reported (Adams & Kubick 1952), the prognosis is considered poor. Patients usually progress to coma and death within days of onset of the illness. Decompressive craniotomy and dehydrating therapy may prolong life by several months, but usually leaves the patient with significant neurologic sequelae (Lamarche et al 1972, Coxe and Luse, 1963). A trial of steroids has been suggested by several authors on theoretical grounds because of the suspected autoimmune nature of the illness (Foley and Kane, 1957; Case Records, NEJM, 1961). In at least one case (Byers, 1975), steroids did seem to be of benefit.

The pathology of AHL is unique, and to date has been the only way of making a definite diagnosis. The white matter of the cerebral hemispheres shows widespread involvement by edema, ball and ring hemorrhages, perivascular exudates, and perivenous foci of microglial proliferation (Gosztonyi, 1978). Zones of demyelination are seen around vessels. The U fibers and subcortical white matter are usually spared, and frontal and parietal lobes tend to be more involved than the temporal lobes. In the brainstem, both white and gray matter may be affected. The etiology of this disease is unknown, though it is felt to be due to an abnormal immune process, with involvement of both cell-mediated and humoral responses (Gosztonyi, 1978; Reik, 1980).

There have been numerous reports of AHL in the literature which have correlated clinical and post-mortem pathological studies. Recently, a case which was clinically consistent with AHL was reported together with the CT scan findings (Reich et al, 1979). However, the diagnosis was not confirmed pathologically. We have recently seen 2 cases of AHL which have allowed us to make further correlations between clinical, radiological and pathological aspects of the disease.

Case 1

A previously healthy 52 year old East Indian woman emigrated to Canada 3 months prior to her hospital admission. 1 month prior to admission, she developed an undiagnosed illness consisting of episodic fever

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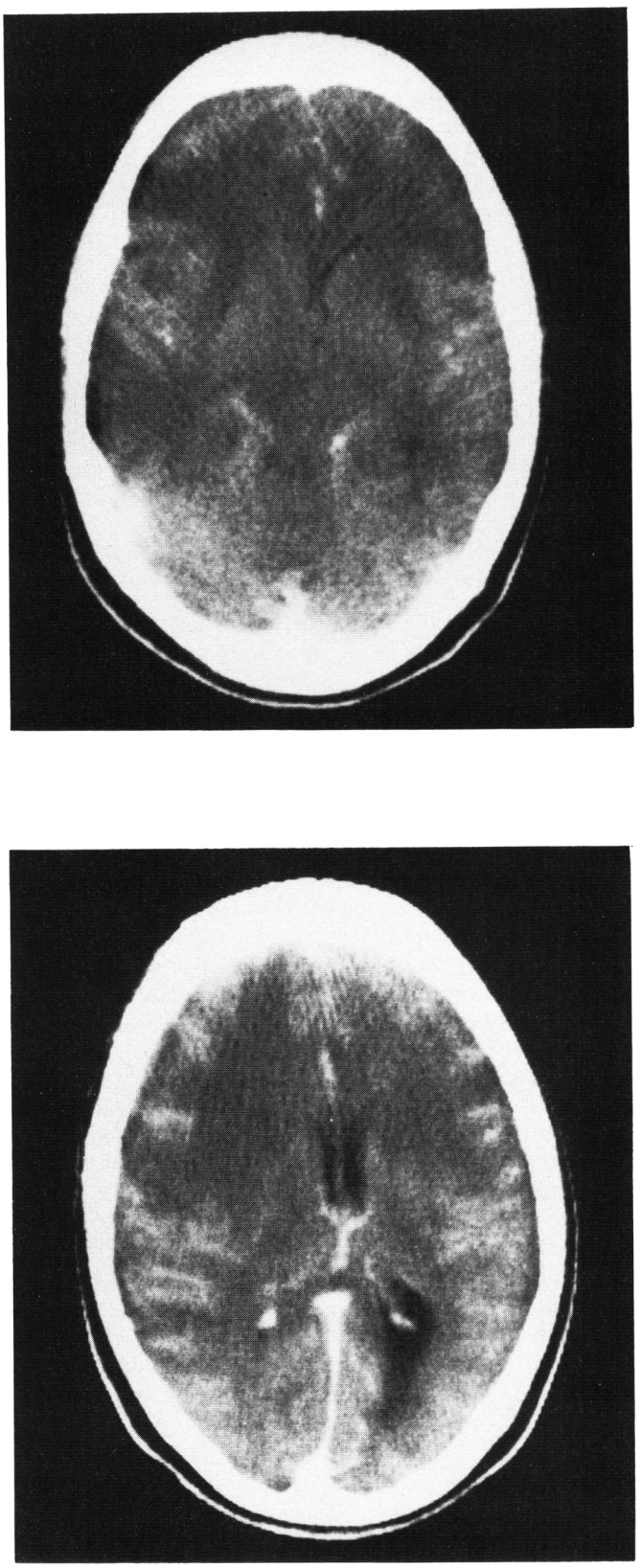

Figure 1 — Case 1: a) Initial CT scan (GE 8800) with contrast shows poorly defined low density changes in both frontal and both temporal lobes, mainly in white matter. No enhancing lesions are seen. b) 3 days after admission CT scan shows marked low density changes primarily in the white matter throughout both hemispheres. There is now compression of the right lateral ventricle with midline shift to the left. Patchy enhancement is present over the cortex.

and chills, which persisted for the whole month. She then developed a continuous fever, headache and confusion, which progressed over a 5 day period, and led to her admission to hospital. General physical examination revealed a pale drowsy woman with a temperature of 38.5°C, but otherwise normal. CNS exam revealed marked neck stiffness. Cranial nerves were considered normal. There was a mild left hemiparesis with a tendency of the patient to look to the right, and a diffuse increase in muscle tone. Reflexes were physiologic and plantar responses were flexor. Bilateral frontal lobe signs could be elicited. Lab investigations: Hg 9.4 g/dl, WBC 6400/cu mm with 69% polymorphonuclears, 17% staff cells, 1% eosinophils, 11% lymphocytes, 2% monocytes. Electrolytes, liver function tests, BUN, creatinine, calcium were all normal. CSF showed protein 130 mg%, glucose 41 mg%, RBC 70/cu mm, WBC 402/cu mm with 72% polys, 38% lympocytes. The opening pressure was 350 mm H_20. Gram stain and culture was negative for bacteria and fungi, and later for TB. Skull x-rays showed a shift of the pineal gland 3-4 mm to the left and opacification of the left maxillary sinus. EEG had background low voltage generalized 4-5 Hz rhythmic activity with superimposed bitemporal moderate voltage 1-3 Hz slow activity, suggesting a diffuse encephalopathy. CT scan showed poorly defined low density changes in the white matter of the frontal and temporal lobes bilaterally (Fig. 1A). No enhancing lesion was seen, though enhancement provided better definition of low density change. Carotid angiography suggested a swelling in the right temporal and right frontal lobes. The patient was diagnosed as having a meningoencephalitis and started on intravenous penicillin and chloramphenicol. INH, streptomycin and rifampin were also added because of the possibility of tuberculous meningitis. A subdural screw was inserted and monitoring showed normal intracranial pressure (ICP). Two hours after this procedure, the patient developed left sided focal seizures and was started on diphenylhydantoin. Over the next 24 hours, the patient developed a marked left hemiplegia, and her right pupil became fixed and dilated. Both plantar responses became upgoing and she became to exhibit decerebrate posturing. Despite intravenous Mannitol and hyperventilation, her condition deteriorated further. She developed gaze palsies, bilaterally decreased corneal reflexes and periods of apnea. ICP was 29. Repeat EEG showed a general deterioration with continuous moderate voltage slow (1-2 cps) activity maximal in the posterior portion of the left hemisphere. A repeat CT scan showed widespread, marked low density changes in the white matter of both cerebral hemispheres, with shift of the midline to the left (Fig. 1B). The patient lapsed into coma, exhibiting right sided myoclonus, generalized seizures, and bilateral fixed dilated pupils. She died on the fifth hospital day.

At autopsy, the only abnormal findings were in the central nervous system. Grossly the brain appeared mildly swollen and there was some herniation of the right temporal uncus. No tonsillar herniation was present. Coronal sections of the cerebral hemispheres revealed widespread

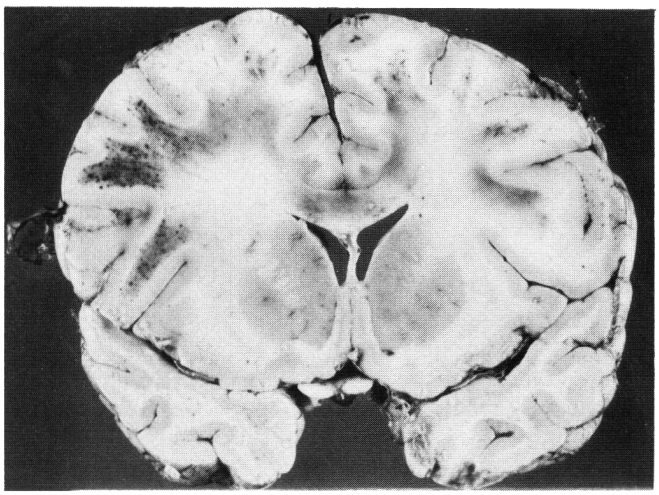

Figure 2 — Case 1: Coronal section through the cerebral hemispheres at the level of the corpus striatum showing bilateral areas of faintly hemorrhagic discoloration in cerebral white matter and corpus callosum as well as some superimposed collections of tiny petechial hemorrhages.

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areas of focal brownish yellow discoloration of white matter, frequently with multiple superimposed tiny petechial hemorrhages. Rarely, these involved grey as well as the white matter. There was similar discoloration present in the corpus callosum. Involvement was bilateral but asymmetrical with more marked involvement in the right than the left hemisphere. (Fig. 2) Horizontal sections of brain stem and cerebellum showed further small focal hemorrhagic or brownish discolored lesions in the lower midbrain and upper pons, involving chiefly the tegmentum.

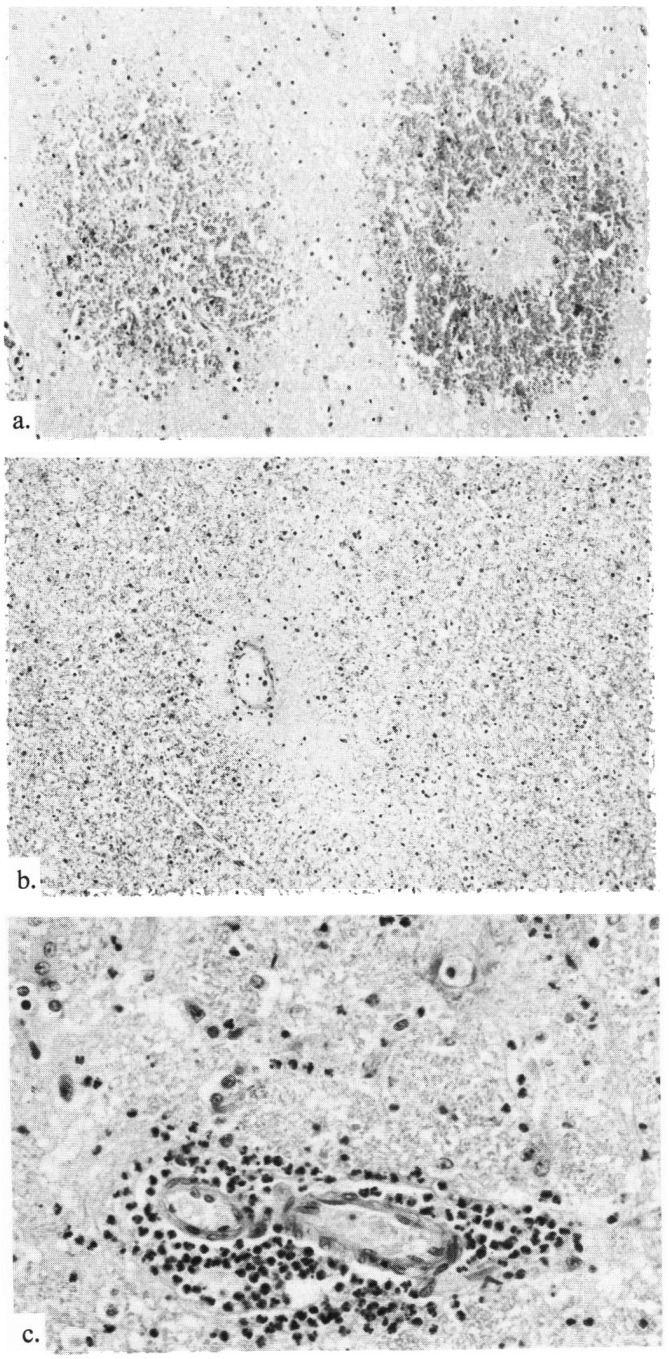

Figure 3 — Case 1: a) Section of frontal white matter showing 2 perivascular hemorrhages centered on small blood vessels. Hematoxylin and eosin, original magnification X 40. b) Parietal lobe white matter showing small perivascular zone of demyelination. Luxol Fast Blue - Cresyl Violet, original magnification X 40. c) Pontine tegmentum showing perivascular accumulation of inflammatory cells, chiefly polymorphonuclear leukocytes. A small blood vessel near the top of the figure also shows some exudation of fibrin into the surrounding brain. Hematoxylin and eosin, original magnification X 100.

Microscopic sections (Fig. 3) showed numerous small, frequently perivascular hemorrhages. In addition, some vessels, chiefly venules, were surrounded by mononuclear and occasionally even polymorphonuclear leukocytes. Occasional vessels exhibited fibrinoid necrosis of their walls and there was some exudation of fibrin into the surrounding brain substance. Rarely, perivenular areas of demyelination were also noted. The changes were noted in sections from the cerebral hemispheres as well as from the brain stem.

Case 2

This previously healthy 61 year old woman developed an upper respiratory tract infection several weeks prior to admission. This was followed by the development of a pneumonia with bronchospasm. She was started on ampicillin, prednisone, and salbutamol. Sudden onset of headache, vertigo, fever and malaise 1 week later, precipitated her admission to hospital. General physical examination at this time was normal.

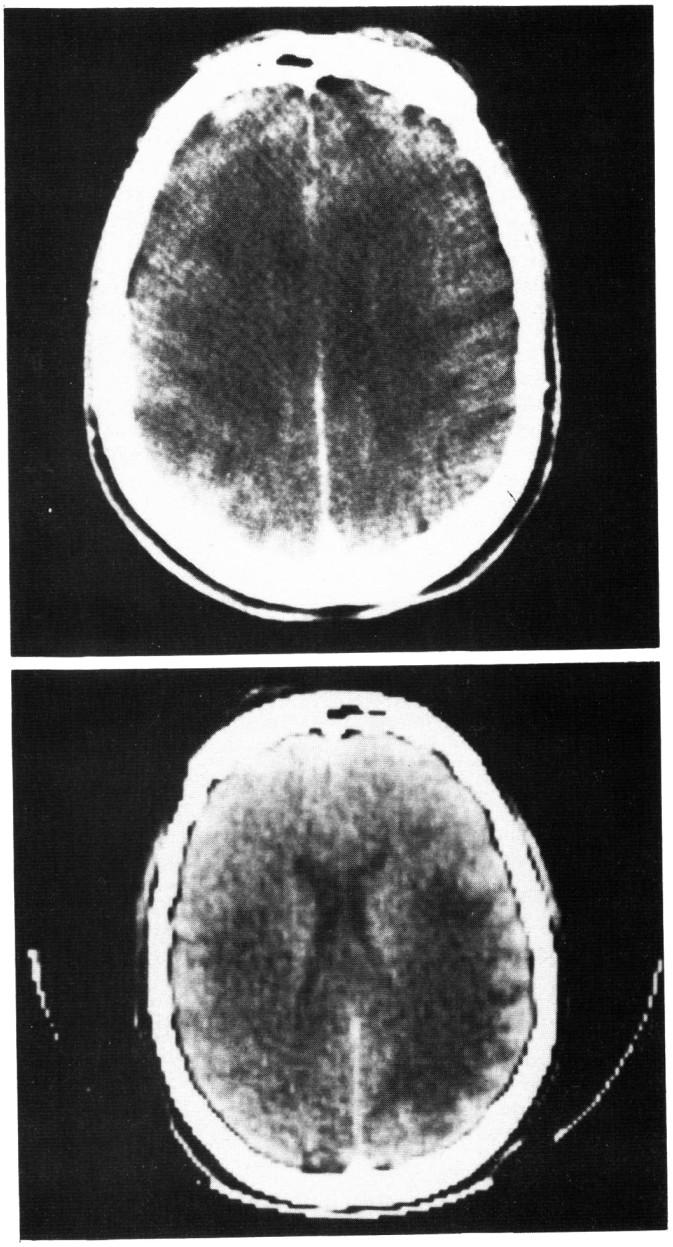

Figure 4 — Case 2: a) CT scan (EMI 1010) with contrast done on ninth hospital day showed widespread low density areas involving only white matter in frontal, parietal, and occipital hemispheres bilaterally, the right more severely affected than the left side. No areas of enhancement are present. b) CT scan 3 weeks after admission shows improvement in white matter abnormalities.

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Neurologic examination revealed a drowsy patient with bilateral horizontal nystagmus, and gait unsteadiness. There were no lateral cerebellar signs. Her neck was supple, and motor and sensory exam was normal. A clinical diagnosis of cerebellar infarction was made. Routine lab investigations were normal and a chest x-ray showed a resolving right middle lobe pneumonia. CT scan done with and without contrast showed no definite abnormality.

The patient was continued on ampicillin and the prednisone was stopped. The patient remained stable for 24 hours, but on the third hospital day, she was noted to be confused. Twelve hours later she was found lying on the floor, stuporous. Her eyes were deviated to the left, but full range of movement was present with Doll's eyes manoeuvre. Bilateral horizontal nystagmus was still present. There was an increase in muscle tone on the left, with a Babinski response present on this side, although there was no hemiparesis. Her neck was supple and fundi were normal. Temperature was 38.2°C. CBC showed Hg 14.0 g/dl, WBC 14,700/cu mm with 78% neutrophils, 11% staffs, 7% lymphocytes, 4% monocytes. ESR was 54. CT scan showed low density change in right occipital and left fronto-parietal areas. A LP was done: opening pressure was 170 mm H_2O. CSF contained 1 RBC, 230 WBC with 96% polymorphs, 4% lymphocytes, protein 87 mg%, glucose 97 mg%, gamma globulin 6.9 mg% (normal to 7.7 mg%), and IgG 10 mg% (normal to 5 mg%). Gram stain, Indian ink preparation, and all cultures were negative. EEG showed a moderate diffuse disturbance in cerebral function with frequent bursts of generalized symmetrical frontal dominant 2-4 cycles per second delta activity and an intermittent low voltage background activity of 4-10 Hz. Radioisotope brain scan and cerebral angiography were normal. The patient was diagnosed as having cerebritis and started on chloramphenicol and ampicillin. Dexamethasone was restarted at 8 mg every 4 hours intravenously. At this time, the patient's condition was deteriorating. She developed bilateral gaze palsies, a diffuse increase in muscle tone, and quadraparesis. The reflexes were pathologically brisk throughout, but plantar responses were now both flexor. She was mute, and would not follow commands. Over the next 48 hours following institution of treatment, her condition began to slowly improve. She remained dysphasic, but started to follow commands and to move her left side well. CT scan was repeated. This showed widespread low density white matter changes in both hemispheres (Fig. 4a). CSF however, showed improvement with protein 56 mg%, glucose 89 mg, WBC 4/cu mm, 2 polymorphs, 2 lymphocytes, gamma-globulin 4.4 mg%, IgG 7 mg%. On the basis of clinical, laboratory, and CT scan information, a diagnosis of AHL was made. Antibiotic therapy was discontinued and she was maintained on 24 mg. of dexamethasone per day. As the patient improved, she continued to exhibit evidence of bilateral cerebral involvement: she had left sided body and visual field neglect, dressing and constructional apraxias, a non-fluent dysphasia, acalculia, and right-left disorientation. She had however, returned to an almost normal level of functioning by the time of her discharge 3 weeks later. Repeat CT scan showed a partial resolution of white matter abnormalities (Fig. 4b). Her CSF, gradually returned to normal as well. All viral studies on blood, stool, urine, throat, and CSF were negative. On a repeat visit $1\frac{1}{2}$ months later, she was found to be functioning at her normal level. Repeat CT scan at this time was normal.

DISCUSSION

The clinical picture in both of these patients fits the previously reported descriptions of AHL. Infectious symptoms were followed by the sudden development of an acute encephalopathy with rapidly decreasing levels of consciousness and signs of bilateral hemispheral and cerebellar involvement. The second case had a slower onset to her disease which may have been due to the course of steroids she received for her brochospasm. Within 24 hours of discontinuation of the steroids she quickly deteriorated, exhibiting typical signs of AHL.

CSF results and EEG in both cases, as well as angiography in the first case were consistent with the diagnosis of AHL. The first case was pathologically confirmed. The second was not, but because of the clinical and laboratory similarities between the two patients as well as to other reported cases, this diagnosis, although presumptive, seems the most likely. Other considerations such as encephalitis due to bacterial or viral causes, infarction, and abscess were ruled out by radiologic and laboratory evaluations.

It has been suggested that an increase in gamma globulin represents the major component of the increase in protein in CSF (Byers, 1975). We had the opportunity to serially study both gamma globulin and IgG in the CSF of our second patient. As reported in the case history the protein was slightly elevated (87 mg%) initially, then gradually fell to a normal level by the time of discharge. Gamma globulin and IgG also followed the same decreasing pattern. However, while gamma globulin remained within the normal range thoughout, IgG was twice the normal value on the initial examination. It would seem that it is the IgG faction that contributes to the rise in protein. Serial determinations of this value may help in following resolution of this disease.

The CT scan changes, which are very similar in both cases, are of particular interest. On admission, case 1 had well-defined areas of low density involving white matter of both hemispheres. Case 2 had a normal CT scan on admission which was the same day as the onset of her illness. The areas of low density did not appear until her third hospital day, but then went on to involve her cerebral hemispheres bilaterally. Contrast was helpful in defining more clearly the localization to white matter, but no definite pattern of enhancement was seen in either case. The areas of radiologic involvement correlated well in both cases with clinical symptoms and signs. In the second case, with recovery from the disease, the CT scan returned to normal over several months as did her neurological deficits. Because of the length of time required for normalization of the scan and the previously described pathological changes of demyelination seen at autopsy, it is felt that, while the early changes seen on CT scan may be due to edema, the persistent areas of low density change must be due to demyelination (Reich et al 1979). Remyelination would lead to a slow normalization of CT scan appearance, and recovery from neurological symptoms.

EEG, radionuclide brain scan, and angiography may be useful in excluding other diseases which may have a similar clinical presentation to AHL, eg. herpes simplex encephalitis, epidural empyema, cerebral abscess. The CT scan, however, is more helpful in that it localizes the radiological changes to white matter, as well as excluding the diseases mentioned. It should be remembered that, as shown above, the CT scan may be normal for up to three days from the beginning of the illness.

Other diseases which affect white matter, such as myelinoclastic diseases of children, the leukodystrophies (Robertson, et al 1977), methotrexate associated leukoencephalopathy (Fusner, et al 1977), progressive multifocal leukoencephalopathy (Carrol, et al 1977) and multiple sclerosis (Cala & Mastaglia, 1976) may present with similar CT scan findings. However, they are easily excluded on clinical grounds. Thus, the CT scan findings in AHL are distinctive, and when combined with the clinical findings, should lead to an early and distinctive diagnosis of this disease.

AHL usually ends in death and only steroids have been reported to have a definite beneficial effect (Byers, 1975). Steroids were started in high doses early in the course of the disease in the second patient, and her recovery seemed to be directly related to their institution. We recommend the use of steroids in high doses whenever this disease is diagnosed.

REFERENCES

Adams, R.D., Cammermeyer, J., and Denny-Brown, D. (1949). Acute necrotizing hemorrhagic encephalopathy. J. Neuropath. Exp. Neurol. 8, 1-29.

Adams, R.D., and Kubik, C.S. (1952). The morbid anatomy of the demyelinative diseases. Amer. J. Med. 12, 510-546.

Behan, P.O., Moore, M.J and Lamarche, J.B. (1973). Acute necrotizing hemorrhagic leukoencephalopathy. Postgrad. Med. 54, 154-160.

Byers, R.K. (1975). Acute hemorrhagic leukoencephalites: Report of three cases of review of literature. Pediatrics 56, 727-735.

Cala, L.A., and Mastaglia, F.L. (1976). Computerized axial tomography in multiple sclerosis. Lancet 1, 689.

Case Records of the Massachusetts General Hospital: Case 48-1961. N. Eng. J. Med. 265, 34-40.

Carrol, B.A., Lane, B., Norman, E., et al. (1977). Diagnosis of progressive multifocal leukoencephalopathy by computed tomography. Radiology 122, 137-141.

Coxe, W.S. and Luse, S.A. (1963). Acute hemorrhagic leukoencephalitis. A clinical and electron-microscopic report of 2 patients treated with surgical decompression. J. Neurosurg. 20, 584-596.

Foley, J.M. and Kane, C.A. (1957). Clinical pathologic conference. Neurology 7, 135-141.

Fusner, J.E., Poplock, D.G., Pizzo, P.A., et al (1977). Leukoencephalopathy following chemotherapy for rhabdomyosarcoma: Reversibility of cerebral changed demonstrated by computed tomography. J. Pediatr. 91, 77-79.

Gosztonyi, G. (1978). Acute hemorrhagic leukoencephalitis in Handbook of Clinical Neurology, 34, 587-604. Ed. Vinken, P.J. and Bruyn, G.W.

Hurst, E.W. (1941). Acute hemorrhagic leukoencephalitis: A previously undefined entity. Med. J. Aust. 28, 1-6.

Lamarche, J.B., Behan, P.O., Segarra, J.M., and Feldman, R.G. (1972). Recurrent acute necrotizing hemorrhagic encephalopathy. Acta. Neuropath. (Berl) 22, 79-87.

Pexman, J.H.N., McFeeley, W.E., and Salmon, M.V. (1974). The angiographic and brain scan findings in acute non-herpetic encephalitis. Brit. J. Radiol. 47, 862-868.

Reich, H., Lin, S.R., and Goldblatt, D. (1979). Computerized tomography in acute hemorrhagic leukoencephalopathy: A case report. Neurology 29, 255-258.

Reik Jr., L. (1980). Disseminated vasculomyelinopathy: An immune complex disease. Ann. Neur. 7, 291-296.

Robertson Jr., W.C., Gomez, H.R., Ruse, D.F., et al. (1977). Computerized tomography in demyelinating disease of the young. Neurology 27, 838-842.