CT in the Early Diagnosis of Herpes Simplex Encephalitis

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Herpes simplex is the most common cause of sporadic viral encephalitis. The recent development of specific antiviral chemotherapeutic agents offers new optimism for patients with this disorder if therapy is begun on or before the fifth day of the disease. Eight patients with herpes simplex encephalitis were studied by CT, and a characteristic but not pathognomonic pattern was observed. In each case a low density lesion was noted in the medial portion of the temporal lobe with extension into the Island of Reil. Sparing of the lenticular nucleus was observed in all cases. Mass effect and streaky linear enhancement after contrast administration was also seen. Unfortunately, the findings may be subtle or absent before the fifth day of disease, and thus CT scans must be examined with a high index of suspicion if the correct diagnosis is to be made at a time when therapy may prove useful. Hemorrhagic areas are rarely observed on CT in this disorder despite the frequent occurrence on pathologic studies. The full extent of involvement may not be appreciated on scans obtained during the first 10 days of the disease.

Herpes simplex is the most common cause of sporadic viral encephalitis [1–3] and morbidity and mortality in this disorder have been extremely high. The recent development of specific antiviral chemotherapeutic agents (e.g., adenine arabinoside) offers new optimism for patients with this disorder [4]. Because these agents have a high morbidity and little or no effect on nonherpetic encephalitis, the diagnosis must be confirmed by brain biopsy prior to instituting therapy. In the past, neuroradiologic procedures such as cerebral angiography and radionuclide scanning have had a role in the diagnosis of this disorder and in determining the optimal site for brain biopsy [5–8]. We report the CT findings in eight patients with confirmed herpes simplex encephalitis and emphasize the characteristic CT pattern identified, the time of appearance, and correlation between CT and pathologic findings.

Materials and Methods

Eight patients with herpes simplex encephalitis (table 1) were studied with CT. In four cases the diagnosis was confirmed pathologically. In one case the virus was isolated from a cerebrospinal fluid specimen, and in three cases a four-fold rise in convalescent cerebrospinal fluid antiherpes titres confirmed the diagnosis. Two of eight patients died postoperatively and were subsequently studied at autopsy. The other six patients are living, but have severe neurologic deficits. The patients were examineed on several CT scanners including the EMI Mark I, EMI 1005, and EMI 5005 scanners. Two patients were studied on the Delta 25 scanner. Follow-up examinations have been obtained in three of four nonsurgical patients. A final follow-up examination was obtained 1–3 months after the onset of symptoms. Noncontrast scans were performed in all eight patients; in seven, contrast-enhanced scans were also obtained.

Quantitative changes in density caused by the disorder were determined. On scans at the level of the suprasellar cistern, the mean densities of the two temporal lobes were determined and compared. On scans obtained at the level of the foramen of Monro, the

Received February 26,1979; accepted after revision August 31, 1979.

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AJR 134:61–66, January 1980
0361–803X/80/1341–0061 $00.00

TABLE 1: **Comparison of Patients with Herpes Simplex Encephalitis**

Case No., Age, and Gender	No. Days from Onset of Symptoms to CT Scan	Radionuclide Scan Results	Method of Diagnostic Confirmation	Surgical Pathologic Findings	Clinical Results
1, 45, M	5, 7, 30, 90	Negative at 7 days	Cerebrospinal fluid titres*	. . .	Seizures and severe intellectual impairment
2, 29, F	5	. . .	Isolation of virus from surgical specimen	Temporal lobe decompression on day 8 showed necrotizing hemorrhagic encephalitis	Moderate hemiparesis; normal mental status
3, 71, M	11, 21, 30	Negative at 3 days; minimally positive at 11 days	Isolation of virus from cerebrospinal fluid	. . .	Mild hemiparesis and severe memory impairment
4, 70, M	5	Not done	Cerebrospinal fluid and blood titres*	. . .	Mental confusion and aphasia
5, 65, F	5	Negative at 6 days	Cerebrospinal fluid titres*	. . .	Mild hemiparesis and aphasia
6, 70, F	9	Negative at 8 days	Isolation of virus from surgical and postmortem specimens	Surgery day 12, temporal lobe decompression. Postmortem at day 13 showed necrotizing hemorrhagic encephalitis involving both temporal lobes and right frontal lobe	Died 13 days after onset of symptoms
7, 48, F	4, 9	Normal at 2 days	Temporal lobe biopsy and culture	Biopsy day 5; temporal lobectomy day 11	Died day 22
8, 19, F	10, 12	. . .	Temporal lobe biopsy and culture	Temporal lobe biopsy; hemorrhagic encephalitis	Moribund

* Four-fold rise in convalescent antiherpes titres

density of the affected medial temporal lobe–Island of Reil region was compared to that of the ipsilateral lenticular nucleus. Density changes after contrast infusion were also identified. In addition, 50 scans in normal adult patients were evaluated by the same method to serve as a control.

Attempts at quantification were limited by several factors including: (1) patients were scanned on more than one unit and CT numbers were not transferable between units; (2) temporal lobes were common sites of artifactual alterations in density; (3) lesions were inhomogeneous with poorly defined margins making it difficult to determine the exact area to be subjected to quantitative analysis.

Results

CT scans in all eight patients demonstrated a characteristic but not pathognomonic pattern (table 2). In each case, low density lesions were noted in the temporal lobes with the greatest effect in the anteromedial part of the temporal lobe and Island of Reil. Abrupt transition to normal density at the lateral margin of the lenticular nucleus was observed in all cases. In case 1 the initial scan (obtained 5 days after the onset of symptoms at an outside institution) demonstrated only a subtle decrease in density of the anterior temporal lobe that was appreciated only in retrospect (fig. 1). In another instance (fig. 2, case 5), bilateral low density in the temporal lobes was identified, but the images were degraded by patient motion and a specific diagnosis was not made.

Three patients initially examined on the EMI 1005 were studied 4–10 days after the onset of symptoms. The affected temporal lobe measured 6.7 Hounsfield units (H) less than the opposite temporal lobe. It measured 11.7 H less than the ipsilateral lenticular nucleus. In the control group, the variation between temporal lobes was 0.8 H, and the temporal lobe measured 2.1 H less than the ipsilateral lenticular nucleus.

TABLE 2: **Summary of CT Findings in Eight Patients**

Findings	Days after Onset of Symptoms			
	0–5	5–15	15–30	30+
Number of cases	5	6	1	3
Bilateral:				
Diffuse edema	0	2	0	0
Bitemporal focal defects	1	0	0	0
Temporal lobe and Island of Reil	5	6	1	3
Lenticular nucleus	0	0	0	0
Contiguous ipsilateral involvement:				
Internal capsule	0	2	1	0
Anterofrontal	3	2	1	0
Frontoparietal	3	4	1	0
Occipital	1	1	0	0
Mass effect:				
Compression	4	5	1	0
Shift	3	5	1	0
Enhancement:				
Para-Sylvian	2/4*	0	1	1
Diffuse gyral blush	0	1	0	0

* One patient scanned without contrast only

Other areas of ipsilateral cerebral hemisphere involvement were noted in contiguity with the temporal lobe lesion. Superior involvement of the frontoparietal area occurred in six cases. Anterior involvement of the inferior frontal lobe was noted in five cases. Posterior involvement of the occipital lobe was seen in three cases while medial involvement of the internal capsule was noted in 2 cases.

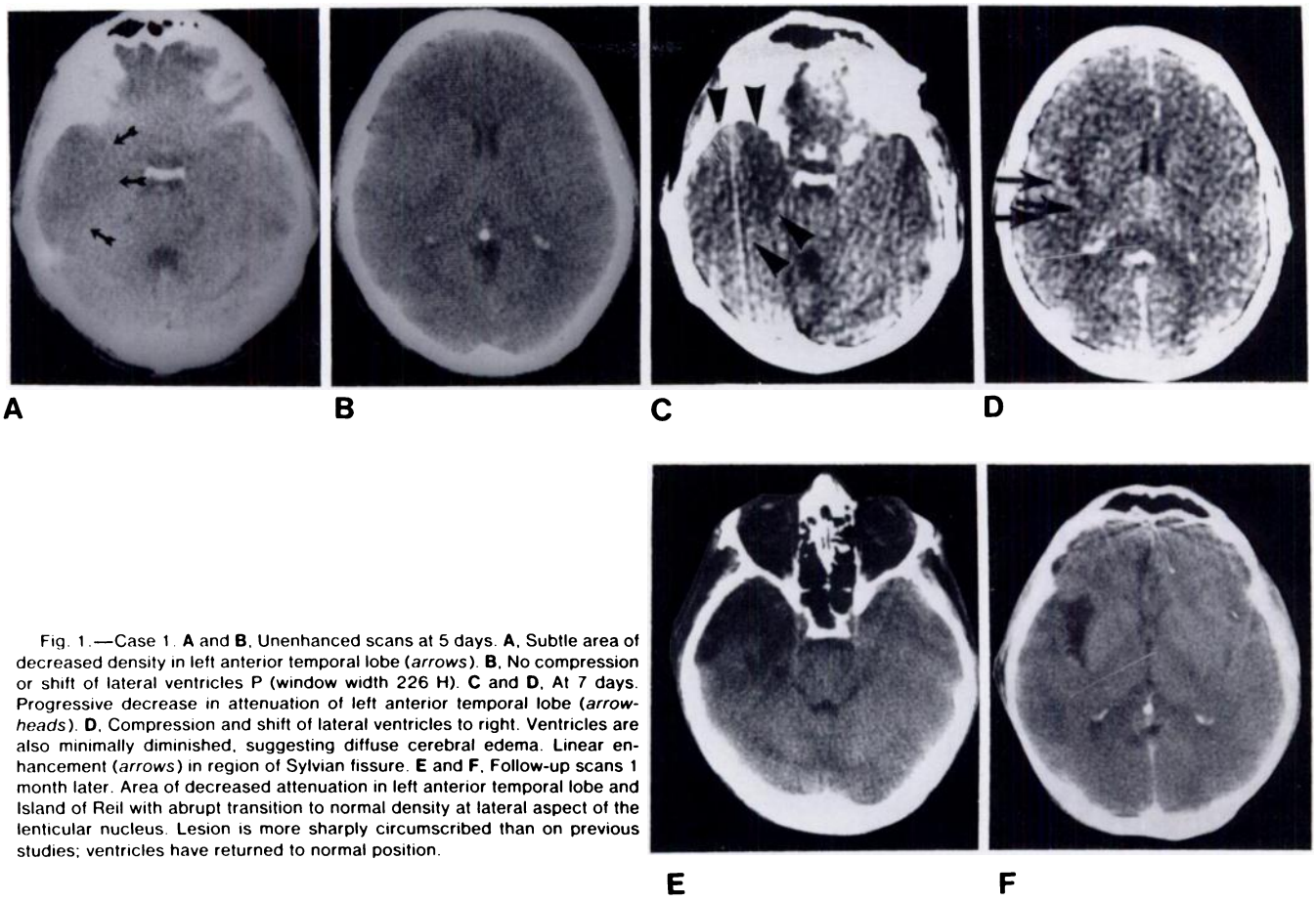

Fig. 1.—Case 1. **A** and **B**, Unenhanced scans at 5 days. **A**, Subtle area of decreased density in left anterior temporal lobe (*arrows*). **B**, No compression or shift of lateral ventricles P (window width 226 H). **C** and **D**, At 7 days. Progressive decrease in attenuation of left anterior temporal lobe (*arrowheads*). **D**, Compression and shift of lateral ventricles to right. Ventricles are also minimally diminished, suggesting diffuse cerebral edema. Linear enhancement (*arrows*) in region of Sylvian fissure. **E** and **F**, Follow-up scans 1 month later. Area of decreased attenuation in left anterior temporal lobe and Island of Reil with abrupt transition to normal density at lateral aspect of the lenticular nucleus. Lesion is more sharply circumscribed than on previous studies; ventricles have returned to normal position.

Diffuse cerebral involvement was noted in cases 1 and 8 (figs. 1 and 3) as manifested by compression of the third and lateral ventricles in both cases, and diffuse enhancement of several gyri after contrast administration in case 3 (fig. 3). In five cases diffuse involvement could not be identified by CT (fig. 4), but bilateral focal temporal lobe involvement was seen in case 5 (fig. 2).

Mass effect with compression of the lateral ventricles was noted on the initial scan in six of eight patients. In case 1, the initial scan, 5 days after the onset of symptoms, demonstrated no mass effect (figs. 1A and 1B), but ventricular compression was noted on a scan 10 days after the onset of symptoms (figs. 1C and 1D). Four cases had midline shift (figs. 3 and 4).

Enhancement was noted on the initial scan of four of seven cases. In case 3 no enhancement was seen on a scan at 11 days, but was identified on a subsequent scan at 29 days (patient not on steroids). The pattern of enhancement was linear and most intense in the region of the Sylvian fissure and Island of Reil (figs. 1 and 3). In three examinations performed on the EMI 1005, the main enhancement of the affected temporal lobe was 14 H.

Follow-up studies on three nonsurgical patients (cases 1, 3, and 5) (fig. 1) demonstrated resolution of mass effect within 1 month of the onset of symptoms. Minimal residual contrast enhancement was observed in one patient examined exactly 1 month after the onset of symptoms; no enhancement was noted in two patients scanned 1 or more months after the onset of symptoms. The lesions became less dense with time (fig. 1). In cases 1 and 3, follow-up scans on the EMI Mark 1, at least 1 month after the onset of symptoms, showed a mean decrease in density of the temporal lobe lesion of 12 H (6 EMI units). This decrease in density resulted in sharper demarcation of the lesion. The areas of contiguous involvement beyond the temporal lobe returned to normal density on subsequent examination producing a more focal residual lesion.

Discussion

Herpes simplex encephalitis is an acute, rapidly progressive disorder which when untreated runs a malignant course resulting in either death or severe mental and physical disability [1–3]. The well known predilection of this disease to involve the temporal lobe [7] is reflected in all eight cases in this series and is consistent with previous descriptions of CT findings in this disorder [9–12]. The areas of greatest involvement were the medial aspects of the temporal lobe

and the Island of Reil. Abrupt transition to normal density at the lateral margin of the lenticular nucleus was noted in all cases, and we suggest this represents a highly characteristic finding, strongly suggestive, but not pathognomonic, of herpes simplex encephalitis. This pattern may be occasionally mimicked by infarction and less commonly by neoplastic lesions such as gliomas (fig. 5).

If chemotherapeutic agents (adenine arabinoside) are to be used successfully, the diagnosis must be established and the treatment begun on or before the fifth day of disease [4]. Therefore, although a characteristic CT pattern is seen, the therapeutic usefulness of identification of this pattern will be limited unless the diagnosis can be made prior to day 5. In this series, four of eight patients were scanned 3–5 days after the onset of symptoms. In each case the scans were positive, but in one case a subtle decrease in density of the temporal lobe was not appreciated initially (case 1, fig. 1). This occurred because the decrease in density was minimal and at least partly obscured by the wide window width (226 H) at which the scan was recorded. It is essential in looking for subtle density alterations to use window settings less than 100 H.

In a second case (case 5, fig. 2), motion artifacts caused areas of decreased attenuation in both temporal lobes creating scans which were considered to be clinically nonspecific. Motion artifacts were a common problem in patients who were either stuporous or uncooperative at the initial study. This problem was exacerbated when longer scanning times were necessary (4 min on the EMI Mark I). Since early diagnosis is essential, heavy sedation or general anesthesia is necessary to obtain high quality scans in patients in whom acute herpes simplex encephalitis is suspected.

In all cases, the initial scan showed a low density lesion, but in two of eight cases (both scanned on or before the fifth day), the initial scan demonstrated no mass effect. Davis et al. [9] reported instances in which scans within 72 hr demonstrated mass effect without a definable area of focal decreased attenuation. Extrapolation from our material and a review of previously reported cases (Davis et al. [9], four cases; Enzman et al. [10], one case) indicated that a normal CT scan prior to the fifth day does not exclude the diagnosis of herpes simplex encephalitis. Moreover, in the approporiate clinical situation, even subtle alterations in density or minimal mass effect in the region of the temporal lobe should be viewed with a high index of suspicion. A specific diagnosis may not be possible on early scans, but CT may indicate the optimal site for diagnostic brain biopsy.

Areas of increased density were absent on precontrast scans in all patients in this series. Pathologic correlation was available in four cases, and in each instance several small areas of hemorrhage were identified. This hemorrhage was not apparent on scans obtained 36 hr or less prior to surgical intervention or death. We believe the discrepancy between CT and pathologic findings is related to the small size of the areas of hemorrhage and because they were always associated with intense edema. On CT the density alterations caused by these two different processes may cancel each other out, thus accounting for the absence of visualization of hemorrhage on CT in this series. In three previous reports [9, 11, 12] with a total of 15 cases scanned within 2 weeks of the onset of symptoms, CT scans showed no evidence of hemorrhage.

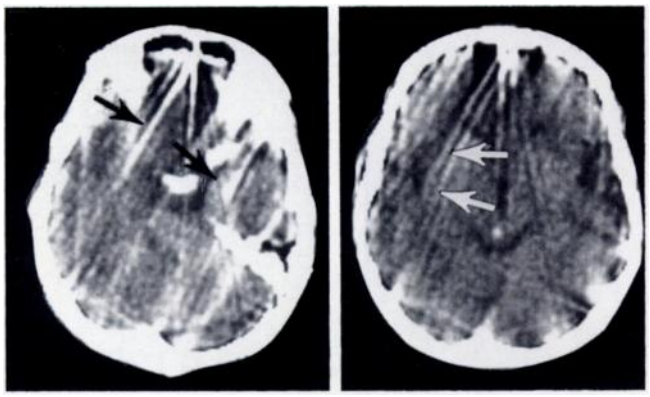

Fig. 2.—Case 5. **A** and **B**, Studies 5 days after onset of symptoms. Hypodensity in both temporal lobes. **B**, No evidence of either midline shift or enhancement. Motion artifacts degrade images. Abruption transition from hypodensity to normal density at lateral ganglionic margin (*arrows*) is typical of herpes encephalitis, but difficult to visualize.

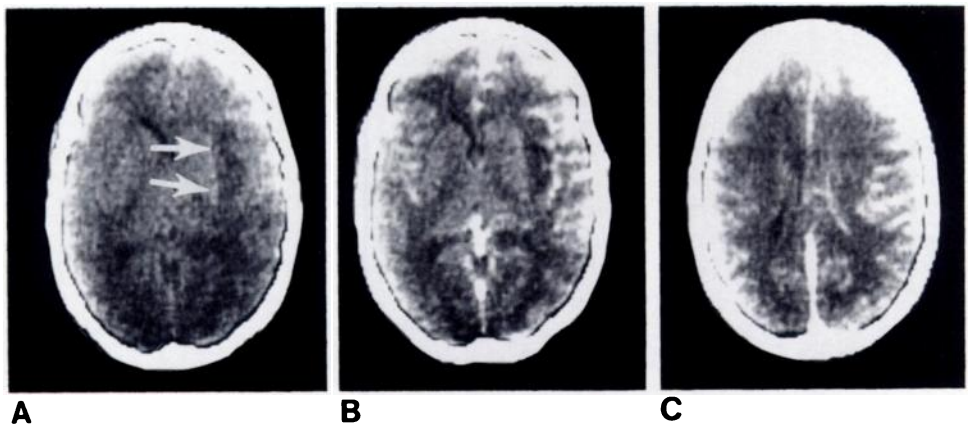

Fig. 3.—Case 8. **A**, Noncontrast scan with focal low density lesion in right temporal lobe and abrupt transition to normal density at lateral ganglionic margin (*arrows*). **B** and **C**, Intense linear enhancement in region of right Sylvian fissure and temporal lobe. At higher levels, diffuse bilateral gyral blush pattern of enhancement is consistent with diffuse cerebritis. Diffuse compression and shift of ventricular system are due to widespread involvement.

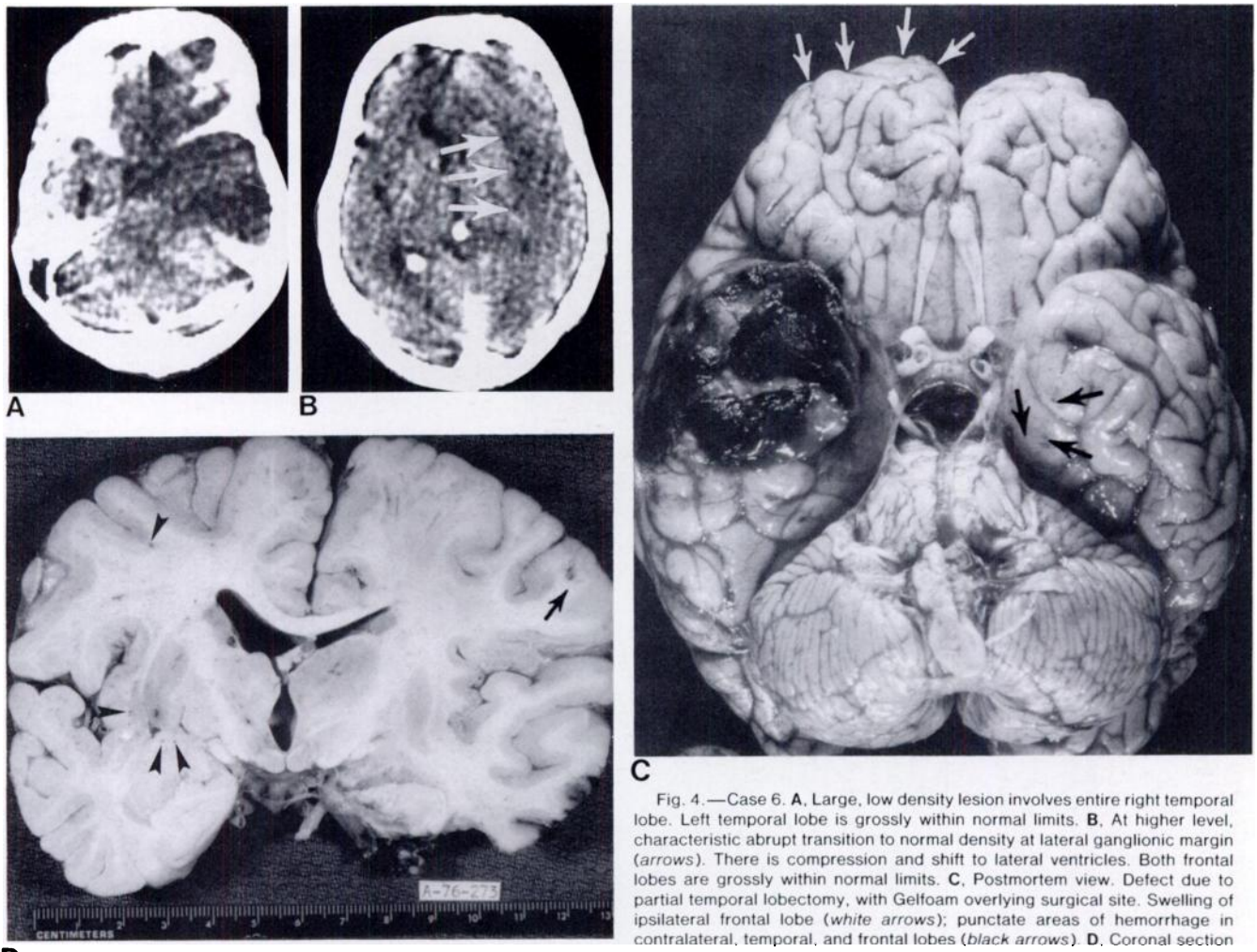

Fig. 4.—Case 6. **A**, Large, low density lesion involves entire right temporal lobe. Left temporal lobe is grossly within normal limits. **B**, At higher level, characteristic abrupt transition to normal density at lateral ganglionic margin (*arrows*). There is compression and shift to lateral ventricles. Both frontal lobes are grossly within normal limits. **C**, Postmortem view. Defect due to partial temporal lobectomy, with Gelfoam overlying surgical site. Swelling of ipsilateral frontal lobe (*white arrows*); punctate areas of hemorrhage in contralateral, temporal, and frontal lobes (*black arrows*). **D**, Coronal section at level of foramen of Monro demonstrates surgical site. Focal area of hemorrhage is on supra-Sylvian ipsilateral frontal lobe (*arrow*); smaller areas of hemorrhage are in contralateral, temporal, and frontal lobes (*arrowheads*).

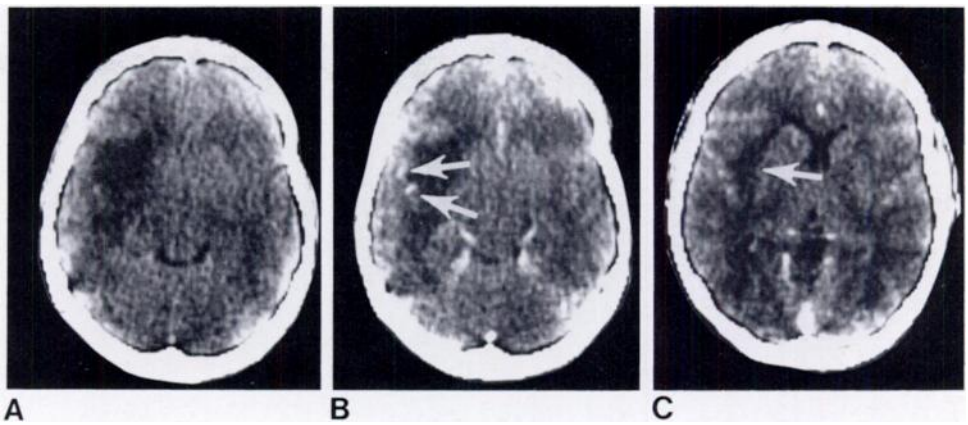

Fig. 5.—Proven glioma simulating herpes simplex encephalitis. **A**, Low density lesion in left temporal lobe on noncontrast scan. **B** and **C**, After contrast infusion. Streaky linear enhancement within lesion (*arrows*). **C**, Abrupt transition to normal density at lateral ganglionic margin (*arrow*). There is mild compression and shift of ventricular system to right.

Enzman et al. [10] reported a high incidence of areas of increased density interpreted as hemorrhage (seven of 13 cases), and this correlated with high erythrocyte counts (more than 1,000 red blood cells/mm^3) in the cerebrospinal fluid. No patient in our series had more than 300 red blood cells/mm^3 in the cerebrospinal fluid. No data are available on cerebrospinal fluid evaluations in the other reports of CT findings in herpes simplex encephalitis [9, 10, 12]. A high

cerebrospinal fluid erythrocyte count is seen in a minority of patients with herpes simplex encephalitis, and often is identified as a late finding in severe or fatal cases of this disease [2].

The patients in the series described by Enzman et al. [10], also showed a higher incidence of diffuse involvement, and a greater mortality rate (five of 13 cases) than in our series (two of eight cases). Enzman and coworkers [10] gathered cases from several institutions, and these may be examples of the most severe manifestations of this disease. Thus, evidence of hemorrhage on CT in herpes simplex encephalitis should be viewed as an uncommon finding and may be indicative of severe involvement by this disorder.

In our series, five of eight patients had unilateral lesions without evidence of either diffuse involvement or focal involvement of the contralateral cerebral hemisphere. In case 6 the CT scan demonstrated only a right temporal lobe lesion, but postmortem examination of the brain revealed bilateral temporal and frontal lobe involvement (fig. 4). Davis et al. [9] showed a higher incidence of diffuse bilateral involvement, but significantly, the diffuse and multifocal component of the disorder was not apparent on CT scans obtained during the first 10 days of the illness, only on follow-up studies. Thus, early in the course of the disease, CT often fails to demonstrate the full extent of the disease process. This failure to document the full extent of the lesion is probably due to the difficulty in detecting large areas of minimally diminished density with poorly defined margins.

Diffuse enhancement after contrast infusion was noted in one patient (case 8, fig. 3). This gyral blush pattern was also seen in several cases reported by Davis et al. [9] and Enzman et al. [10]. It represents a diffuse cerebritis and/or meningitis.

In this series, follow-up studies in three cases demonstrated resolution of mass effect and enhancement after 1 month. On delayed scans a sharply etched, low density lesion was seen in the medial temporal lobe, with total resolution of abnormal densities noted in areas outside the temporal lobe. Large areas of residual low density were not noted in three patients on whom follow-up scans were obtained in this series, but they have been observed in other patients; in particular, when there was evidence of diffuse involvement on earlier CT scans [9, 10, 12].

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