

LA CROSSE ENCEPHALITIS IN CHILDREN

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ABSTRACT

Background La Crosse encephalitis is a mosquito-borne disease that can be mistaken for herpes simplex encephalitis. It has been reported in 28 states but may be underrecognized.

Methods We investigated the manifestations and clinical course of La Crosse encephalitis in 127 patients hospitalized from 1987 through 1996. The diagnosis was established by serologic testing for IgM and IgG antibodies to La Crosse virus. Data were collected by chart review.

Results Most of the patients were school-aged children (mean [\pm SD] age, 7.8 ± 3.5 years; range, 0.5 to 15.0). Symptoms included headache, fever, and vomiting (each in 70 percent or more of the patients), seizures (in 46 percent), and disorientation (in 42 percent). Thirteen percent had aseptic meningitis. Hyponatremia developed in 21 percent, and there were signs of increased intracranial pressure in 13 percent. Six patients, including three with cerebral herniation, underwent intracranial-pressure monitoring. The 13 patients (11 percent) whose condition deteriorated in the hospital had decreases in serum sodium levels ($P=0.007$) and increases in body temperature ($P=0.003$) at the time of deterioration. At admission, these patients more often had a history of vomiting ($P=0.047$) and a score of 12 or lower on the Glasgow Coma Scale ($P=0.02$) than the others; a trend toward a greater prevalence of seizures at admission was also evident in this group ($P=0.07$). All the patients survived, but 15 of them (12 percent) had neurologic deficits at discharge. Follow-up assessments, performed in 28 children, suggested an increase in cognitive and behavioral deficits 10 to 18 months after the episode of encephalitis.

Conclusions La Crosse virus infection should be considered in children who present with aseptic meningitis or encephalitis. Hyponatremia and increasing body temperature may be related to clinical deterioration. (N Engl J Med 2001;344:801-7.)

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LA CROSSE virus is the most pathogenic member of the California encephalitis serogroup. It was first isolated from the brain of a four-year-old child who had died of "rural encephalitis" in La Crosse County, Wisconsin.¹ The virus is transmitted by the tree-hole mosquito, *Aedes triseriatus*, and causes the most prevalent arboviral infection in children in North America.¹⁻⁷ Nevertheless, La Crosse encephalitis often goes unrecognized. The

virus typically cannot be recovered from cerebrospinal fluid, and the disease can masquerade as enteroviral meningitis when mild and as herpes simplex encephalitis when severe.⁸⁻¹⁴ Currently, there is no antiviral therapy that has been approved by the Food and Drug Administration (FDA) for La Crosse encephalitis.

The death of a child with La Crosse encephalitis at the Charleston Area Medical Center in West Virginia in 1987 spurred the establishment of a surveillance program, which revealed the disease to be highly endemic in West Virginia, with an incidence (20 to 30 cases per 100,000 children less than 15 years of age) similar to that in areas of endemic disease in the Midwest.¹⁵⁻¹⁸ Over a 10-year period, we treated 127 inpatients with La Crosse encephalitis.

The objectives of this study were to provide an updated description of the manifestations and management of this disease and to identify factors associated with clinical deterioration.^{1,16}

METHODS**Patients**

Data on patients who were admitted to the Charleston Area Medical Center with La Crosse encephalitis from 1987 through 1996 were reviewed with use of a data-collection instrument designed in 1990. Criteria for inclusion in the study were clinical evidence of meningitis or encephalitis (seizures, disorientation, coma, or focal neurologic signs); an elevated white-cell count in the cerebrospinal fluid; and a serum titer of IgM antibody to La Crosse virus of at least 1:10, a serum titer of IgG antibody to La Crosse virus of at least 1:160, or both; or an increase in the serum titer of antibody to La Crosse virus to at least four times its value at the time of admission. Serum IgM and IgG antibodies to La Crosse virus were detected by indirect immunofluorescence.¹⁹

Statistical Analysis

We used Student's *t*-test or analysis of variance for continuous variables, the chi-square test or Fisher's exact test for categorical variables, and nonparametric methods as appropriate. For continuous variables, means and standard deviations are reported for descriptive statistics, whereas means and standard errors are reported for comparative analyses. Univariate analyses were performed to identify clinical and laboratory variables at admission that were associated with in-hospital deterioration. Seven patients began receiving investigational antiviral therapy (or placebo) for symptoms present at admission and were excluded from the univariate analysis.

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ses; six patients began such therapy after admission (and after clinical deterioration) and remained in the analyses. These 13 patients were excluded from analyses of the following: the number of days hospitalized and the number of hours hospitalized before resolution of fever; the rate of resolution of fever; the number of days in the pediatric intensive care unit; and the number of hours intubated.

RESULTS

Patients

A total of 127 children met the criteria for inclusion in the study. None of the viral cultures of cerebrospinal fluid, obtained from 107 patients (84 percent), were positive for La Crosse virus, although the virus was isolated from a brain-biopsy specimen from one patient.¹⁹ Most cases occurred from July through September in school-aged children (mean [\pm SD] age, 7.8 ± 3.5 years; range, 0.5 to 15.0), the majority of whom were boys (Table 1). Thirty-two percent of the children had been referred from other hospitals. Their

symptoms included headache, fever, and vomiting (each in 70 percent or more of the patients) and disorientation (in 42 percent). Seizures were the presenting finding in 58 of the patients (46 percent). Of those with seizures, 14 (24 percent) had status epilepticus, and 36 (62 percent) had seizures with a focal component. Pertinent negative physical findings included the absence of exanthem (in 119 of the patients [94 percent]) and of enanthem (in 124 [98 percent]). Of the 33 patients (26 percent) who had signs of meningeal involvement, about half (17 patients [13 percent]) had aseptic meningitis and half (16 patients [13 percent]) had meningoencephalitis.

Laboratory Findings

On initial lumbar puncture, 13 of the patients (10 percent) had white-cell counts below 10 per cubic millimeter. Initial peripheral white-cell counts were elevated ($>15,000$ per cubic millimeter) in 62 of the patients (49 percent), with polymorphonuclear cells predominating (Table 2). Hyponatremia, defined as a serum sodium level below 132 mmol per liter (consistent with a serum osmolality of <275 mOsm per kilogram of water in most children), was present in 27 of the patients (21 percent). In 8 of these 27 patients, urine electrolyte concentrations and osmolality or specific gravity were measured, and in all but 1 the results were consistent with the syndrome of inappropriate antidiuretic hormone secretion.

Electroencephalographic Findings

Of the 90 patients who underwent electroencephalography (71 percent), 59 had abnormal tracings; there was slight slowing in 18, moderate to severe slowing in 15, focal slowing in 15, periodic lateralizing epileptiform discharges in 8, and focal epileptiform discharges in 3. Of the abnormal electroencephalograms, 26 had features that suggested herpes simplex encephalitis, such as focal features (in 18) or periodic lateralizing epileptiform discharges, usually with involvement of the temporal lobe (in 8). Continuous electroencephalographic monitoring was necessary in four patients with periodic lateralizing epileptiform discharges, and sufficient control was achieved with bolus injections of phenobarbital (in addition to midazolam and phenytoin) and, in one patient, with a continuous infusion of midazolam.

Radiographic Findings

Computed tomographic (CT) scans were obtained in 92 of the 127 children. In only 11 of these 92 children (12 percent) were there abnormalities on the scans; generalized cerebral edema was the most common finding (in 8 patients) (Fig. 1A). In three children with initially normal CT scans, abnormalities were noted only after cerebral herniation: two had generalized edema (Fig. 1A), and one had multifocal edema (Fig. 1B).

TABLE 1. EPIDEMIOLOGIC AND CLINICAL DATA ON 127 CHILDREN WITH LA CROSSE ENCEPHALITIS.*

VARIABLE	VALUE
Sex — no. (%)	
Male	90 (71)
Female	37 (29)
Age — no. (%)	
0.5–2 yr	9 (7)
3–5 yr	30 (24)
6–8 yr	42 (33)
9–11 yr	26 (20)
12–14 yr	19 (15)
15 yr	1 (1)
Month of presentation — no. (%)	
June	3 (2)
July	31 (24)
August	38 (30)
September	44 (35)
October	11 (9)
Symptoms on presentation — no. with finding/total no. (%)†	
Headache	105/126 (83)
Fever	107/125 (86)
Vomiting	89/127 (70)
Disorientation	50/119 (42)
Seizures‡	58/127 (46)
Signs on admission — no. with finding/total no. (%)	
Nuchal rigidity	31/120 (26)
Glasgow Coma score ≤ 12	42/127 (33)
Focal neurologic signs	23/126 (18)

*For symptoms on presentation and signs on admission, data were missing for some patients. Because of rounding, not all percentages total 100.

†Typically, the patients with headache or fever were admitted three or four days after presentation; those with vomiting were admitted one or two days after presentation; and those with disorientation or seizures were admitted on the day of presentation.

‡Seizures were generalized in 22 patients, partial in 24, and partial with secondary generalization in 12.

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TABLE 2. LABORATORY VALUES AT ADMISSION IN PATIENTS WITH LA CROSSE ENCEPHALITIS.

VARIABLE	MEAN VALUE ±SD	RANGE	PERCENTILE					REMARKS
			10TH	25TH	50TH	75TH	90TH	
Cerebrospinal fluid								
White-cell count (per mm ³)	130±151	2-867	10	26	75	184	316	<200/mm ³ in most cases
Differential count (% lymphocytes)	—	2-100	10	27	62	77	90	Predominance of lymphocytes
Red-cell count (per mm ³)	71±213	0-1500	0	1	5	20	177	Elevated (≥20/mm ³) in 25%
Glucose (mg/dl)*	75±20	37-149	56	62	71	83	105	Normal
Protein (mg/dl)	37±15	10-85	20	27	34	45	56	Rarely elevated
Peripheral blood								
White-cell count (per mm ³)	15,700±5900	6800-49,700	8900	11,500	14,800	19,000	22,600	Usually elevated (>15,000/mm ³)
Differential count (% polymorphonuclear leukocytes)	—	17-94	58	66	76	82	86	Predominance of polymorphonuclear leukocytes

*To convert values for glucose to millimoles per liter, multiply by 0.05551.

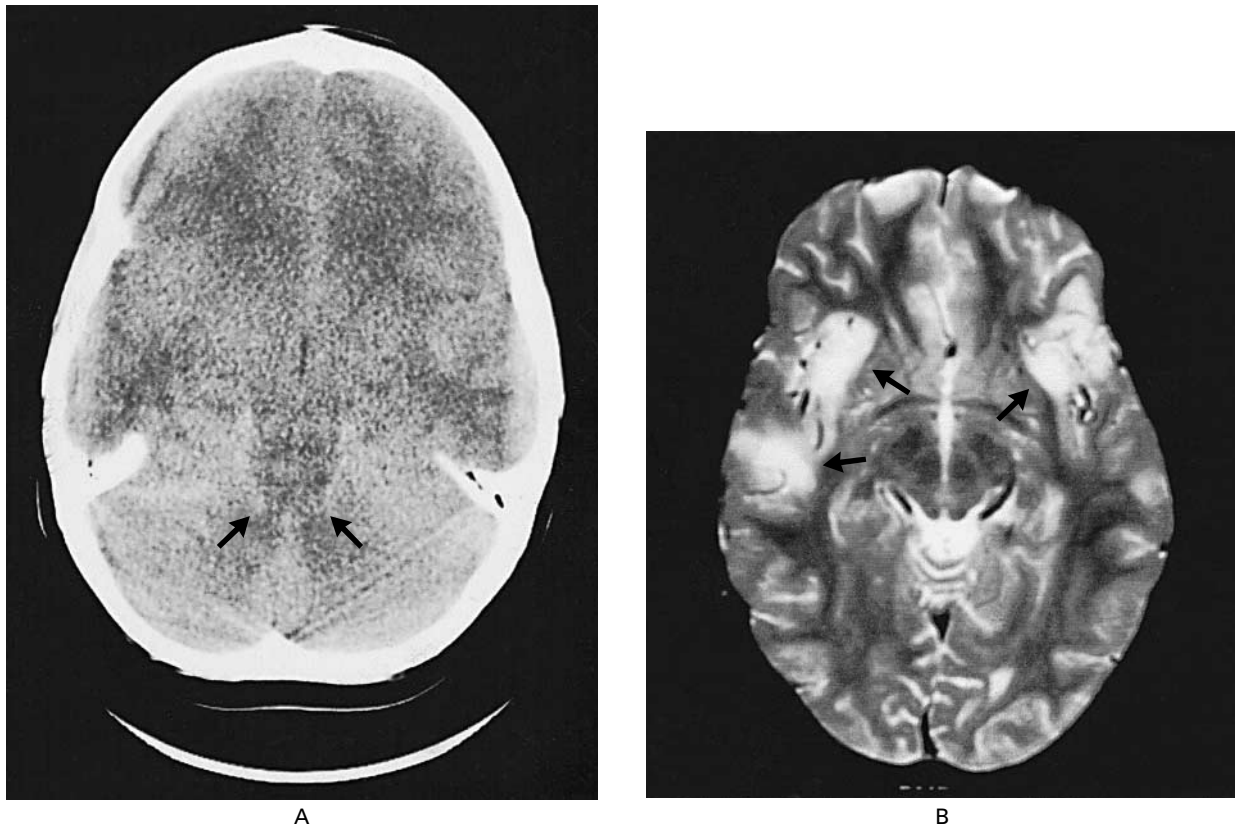


Figure 1. Radiographic Studies in Patients with Severe La Crosse Encephalitis.

In Panel A, a CT scan of an eight-year-old boy with severe La Crosse encephalitis complicated by uncal herniation (obtained on the second hospital day) reveals brain edema with associated obliteration of perimesencephalic cisterns (arrows). In Panel B, a T₂-weighted magnetic resonance image obtained in a seven-year-old boy with severe La Crosse encephalitis shows focal areas of increased signal intensity in the right temporoparietal and left frontotemporal regions (arrows). A CT scan obtained at the time of uncal herniation seven days earlier showed hypodensity in the same areas.

Magnetic resonance imaging of the head was performed in 10 patients with severe disease. In four of them the results were abnormal, with focal areas of gadolinium enhancement, predominantly in cortical areas (Fig. 1B).

Hospital Course and Complications

The duration of illness and fever and the timing of interventions are shown in Table 3. Complications during hospitalization included hyponatremia in 27 patients (21 percent); seizures in 16 (13 percent), 4 of whom had status epilepticus; and signs of increased intracranial pressure in 16 (13 percent), 3 of whom had cerebral (uncal) herniation.

In the three children with cerebral herniation, the herniation episodes occurred within 36 to 72 hours after admission. Each of these children had had seizures at the time of admission. In two of them, disorientation had progressed to coma during the 6 to 12 hours before herniation, but in the third only disorientation was present before the event. In two of these patients, intraparenchymal intracranial-pressure monitoring showed sustained increases in intracranial pressure to levels as high as 20 to 30 mm Hg; in the third, protracted elevation of the intracranial pressure (to 40 to 50 mm Hg) necessitated intraventricular pressure monitoring for nine days. These three patients received treatment with intravenous ribavirin after approval for its emergency use had been obtained from the FDA.

Critical Care Interventions

Seventy-two of the patients (57 percent) were admitted to the pediatric intensive care unit, 32 (25 per-

cent) required mechanical ventilation, 17 (13 percent) received mannitol, 6 (5 percent) had intracranial-pressure monitoring, and 1 (1 percent) underwent a brain biopsy. Two patients with cerebral herniation received inotropic support, one during the treatment of intracranial pressure with pentobarbital-induced coma and hypothermia. A brain biopsy was performed for suspected herpes simplex encephalitis in one patient with severe disease, in whom assays for IgM antibodies to La Crosse virus were initially negative.¹⁸ Direct immunofluorescence of the biopsy specimen revealed the presence of La Crosse virus antigen (Fig. 2).

Factors Associated with Deterioration

All the patients who were admitted, except the seven who began receiving investigational antiviral treatment (or placebo) for symptoms present at the time of admission, were considered at risk for clinical deterioration. In-hospital clinical deterioration was defined as a marked change in neurologic status that developed after admission and that required definitive intervention in addition to monitoring. Such deterioration occurred in 13 patients (11 percent) within four days after admission, prompting endotracheal intubation in 9. The neurologic events in these patients included cerebral herniation (in three patients), status epilepticus (in six), generalized seizure lasting more than 10 minutes (in one), partial seizures (in two), and deep coma with depressed respirations (in one).

Factors associated with in-hospital deterioration included a history of vomiting, which was present in 12 of the 13 patients with deterioration, as compared with 70 of the other 107 patients ($P=0.047$), and a trend toward seizures at presentation (which were present in 9 of these 13 patients vs. 46 of the other 107; $P=0.07$). After the exclusion of 22 patients who had undergone intubation at admission and 9 whose condition was postictal, those with deterioration had a lower score on the Glasgow Coma Scale at admission than those without deterioration (median score, 13 vs. 15; $P=0.01$ by the Mann-Whitney U test) and more often had a score of 12 or less (5 of 10 patients vs. 13 of 86; $P=0.02$ by Fisher's exact test). (The scores on this scale range from 3, indicating the absence of verbal, motor, or eye-opening responses, to 15, indicating complete responsiveness and orientation.)

In the patients with in-hospital deterioration, the nadir serum sodium level during hospitalization was slightly lower than in those without deterioration (131.9 ± 0.8 vs. 133.8 ± 0.3 mmol per liter, $P=0.02$ by Student's t-test). Their mean serum sodium level declined from 138.2 ± 1.2 mmol per liter at the preceding measurement to 134.2 ± 1.3 mmol per liter at the time of the deterioration ($P=0.007$ by the paired Student's t-test). Furthermore, in 6 of the 13 with deterioration, the serum sodium level at the time of deterioration decreased to within 1 mmol per liter of the nadir during the entire period of hospitalization;

TABLE 3. TIME COURSE OF ILLNESS AND FEVER AND DURATION OF INTERVENTIONS IN PATIENTS WITH LA CROSSE ENCEPHALITIS.

VARIABLE	NO. OF PATIENTS	MEAN (\pm SD) NO. OF DAYS
Course of illness		
Illness before admission	127	3.4 \pm 2.3
Hospitalization*	114	6.2 \pm 3.1
Hospitalization before resolution of fever†	98	2.5 \pm 1.6
Interventions		
Stay in pediatric intensive care unit*	59	3.0 \pm 1.6
Intubation*	22	2.1 \pm 1.8
Treatment with antibiotics	94	3.9 \pm 2.4
Treatment with acyclovir	28	3.7 \pm 3.1

*The 13 patients who received investigational antiviral therapy (or placebo) were excluded.

†Fever had resolved in 70 percent of the patients after three days and in 90 percent of the patients after seven days. The 13 patients who received investigational antiviral therapy (or placebo) were excluded, as were the 17 without documented fever after admission.

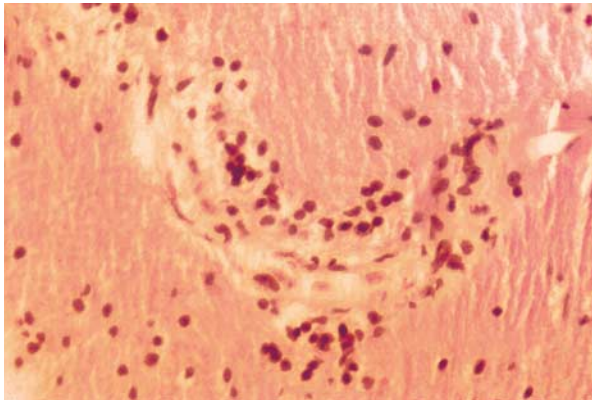


Figure 2. Brain-Biopsy Specimen from a Seven-Year-Old Boy with Severe La Crosse Encephalitis (Hematoxylin and Eosin, $\times 200$).

Perivascular infiltration with mononuclear cells is present on light microscopy. This biopsy material was positive for La Crosse virus antigen on direct immunofluorescence assay.¹⁸

among these 6 were 5 with nadir values of 130 mmol per liter or less (2 of whom had cerebral herniation).

In the 13 patients with clinical deterioration, the body temperature had increased from a mean of $37.3 \pm 0.3^\circ\text{C}$ and $37.5 \pm 0.2^\circ\text{C}$ (at eight and four hours, respectively, before the deterioration) to 38.2 ± 0.3 at the time of the deterioration ($P < 0.01$ by repeated-measures analysis of variance). In 7 of the 13, the temperature exceeded 38.5°C ; in 3 of these 7 it exceeded 39°C .

Neurologic Deficits

At discharge, 15 children (12 percent) had neurologic deficits. These included sixth-nerve palsy and hemiparesis in two, mild hemiparesis in one, speech problems in three, aphasia in one, decreased short-term memory in four, behavioral problems or dull affect in three, and poor balance in one. Preliminary neurobehavioral follow-up data were obtained for 28 (32 percent) of the 88 children more than five years of age, a group with relatively severe disease. Cognitive testing with the Wechsler Intelligence Scale for Children, third edition, was performed in these 28 children 10 to 18 months after hospitalization for encephalitis. Their mean full-scale IQ score was 87.8 ± 15.1 (95 percent confidence interval, 82.2 to 93.2), which is significantly below the assumed population mean of 100 ($P < 0.001$ by Student's *t*-test).^{20,21} Mean scores on the verbal and performance subscale IQ tests were similarly depressed (87.9 ± 17.9 and 89.3 ± 15.4 , respectively). Ten of the 28 children had IQ scores indicating either borderline intelligence (a score of 70 to 79, in 7 children) or mental retardation (a score of < 70 , in 3 children). There were large dis-

parities (≥ 12 points) between the verbal and performance scores of 13 of the tested children.²⁰ Of the 25 children evaluated for attention-deficit-hyperactivity disorder, 15 had results indicating the presence of the disorder.^{22,23}

DISCUSSION

La Crosse encephalitis has been reported in 28 states, and in areas where the disease is endemic the incidence exceeds that of bacterial meningitis before the introduction of the *Haemophilus influenzae* vaccine.^{15,16} Our experience suggests that La Crosse encephalitis may be underrecognized not only in terms of its prevalence but also in terms of its severity: about one in four of our patients required intubation, about one in four of those with seizures had status epilepticus, and three (2.4 percent) had cerebral herniation.

Previous reports have indicated that at presentation, 42 to 62 percent of hospitalized patients had seizures and 16 to 25 percent had focal neurologic abnormalities, findings similar to our experience.⁹⁻¹⁴ The typical patient in our population was a school-aged boy who presented with fever and headache that had begun three to four days previously, with progression to vomiting for one or two days and disorientation or seizures on the day of admission (Table 1). The average duration of hospitalization was six days, and most of the children became afebrile by the third hospital day. Our data confirm that La Crosse encephalitis may mimic herpes simplex encephalitis, with fever, focal signs, or focal seizures (or focal electroencephalographic changes) in roughly half the patients and hemorrhagic pleocytosis in about one fourth. Furthermore, eight of our patients had periodic lateralizing epileptiform discharges, previously thought to be highly characteristic of herpes simplex encephalitis.^{24,25}

Milder forms of La Crosse encephalitis may be confused not only with enteroviral meningitis²⁶ but also with partially treated bacterial meningitis, because in La Crosse infection peripheral white-cell counts are often elevated. In addition, the serum level of C-reactive protein, which when elevated is generally considered to indicate bacterial infection,²⁷ was elevated in 12 of the 26 patients in our study in whom it was measured. This disease is also difficult to recognize because the virus is rarely isolated from the cerebrospinal fluid.⁸ Serologic analysis by indirect immunofluorescence is a sound method for the detection of IgM and IgG antibodies to La Crosse virus, with adequate sensitivity (82 to 93 percent) and high specificity (approaching 100 percent), provided that criteria for reading the results are stringent.^{19,28} Use of the polymerase chain reaction for the diagnosis of La Crosse encephalitis is still at a research stage.²⁹⁻³¹ The ability to diagnose La Crosse encephalitis helped to reduce the duration of treatment of presumed herpes simplex encephalitis with acyclovir or presumed bacterial meningitis with antibiotics (Table 3). Acyclovir,

which was initially given to 28 of the 127 patients for presumed herpes simplex encephalitis, has no inhibitory effect on La Crosse virus, which is an RNA virus. Since there is evidence of inhibition of La Crosse virus by ribavirin, we have piloted its use as compassionate therapy. We are currently investigating the use of intravenous ribavirin in a randomized clinical trial in patients with severe disease.^{19,32}

Approximately 10 percent of the patients admitted to our institution had neurologic deterioration during the first four hospital days. The finding that patients with deterioration were more likely to have a score on the Glasgow Coma Scale of 12 or lower at admission is useful, because such a score typically indicates changes in mental status, which in turn usually signal the need for monitoring in the intensive care unit.³³ If a conservative approach is taken, intensive care monitoring could also be considered for patients who present with seizures. A history of vomiting is such a common finding (occurring in 71 percent of the patients in this study) that it is not useful for clinical decision making.

The temporal relation between hyponatremia and clinical deterioration and between fever and clinical deterioration suggests that these factors may play a part in central nervous system injury by lowering the threshold for seizures or by exacerbating intracranial hypertension. The literature supports the concept that these factors can potentiate increases in intracranial pressure.³⁴⁻⁴⁸

It may be appropriate to manage La Crosse encephalitis, and perhaps central nervous system infections in general, with some of the measures currently used in children at risk for increased intracranial pressure. For example, isotonic intravenous fluids (such as normal saline) are recommended in the initial treatment of patients with closed head injuries and diabetic ketoacidosis, but such recommendations have not yet been extended to central nervous system infections.^{47,49,50} This approach seems particularly prudent in view of the recent recommendation to avoid early restriction of fluids in children with such infections, pending evidence to support the diagnosis of the syndrome of inappropriate antidiuretic hormone secretion.⁵⁰ Measures used to prevent or treat fever, such as those used in children with suspected or confirmed intracranial hypertension, should also be considered^{51,52}; these may include the judicious use of cooling blankets (provided that shivering can be prevented or treated) with continuous monitoring of body temperature.

Preliminary findings indicating a depression in full-scale IQ scores and in verbal and performance subscale scores differ from the results of previous studies of children who have recovered from encephalitis, which reported IQ scores in the range of 96 to 110, although each study indicated that those with more severe disease were more likely to have cognitive deficits.^{53,54} The degree of cognitive impairment in the

patients in our series (36 percent of whom had a full-scale IQ score of 79 or less), as well as the high incidence of attention-deficit-hyperactivity disorder (60 percent of those tested),⁵⁵ suggests that neurobehavioral effects can develop after La Crosse encephalitis.

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