

Neurological Complications of Hemolytic-Uremic Syndrome

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Abstract

Of 78 children identified with hemolytic-uremic syndrome at the Children's Hospital, Boston, from 1976 to 1986, 16 patients (20.5%) had neurological manifestations during their hospitalization. The most common manifestations were significant alterations in consciousness (coma, stupor) in 12 patients, and either generalized or partial seizures in ten patients. Others included hemiplegia (4 patients), decerebrate posturing (3), cortical blindness (2), hallucinations (1), and dystonic posturing (1). Cranial computed tomographic scans were abnormal in eight of 11 patients scanned. The abnormalities included diffuse cerebral edema (4 patients), large vessel infarctions (3), diffuse multiple small infarcts (4), and multiple hemorrhages (1). Five patients died as a result of their central nervous system complications, and six had neurological sequelae at discharge. Five patients recovered and at discharge had no evidence of neurological dysfunction. (*J Child Neurol* 1989;4:108-113).

Hemolytic-uremic syndrome is defined by the presence of microangiopathic hemolytic anemia, thrombocytopenia, and acute oligoanuric renal failure. Hemolytic-uremic syndrome occurs most frequently in children younger than 5 years old, although the syndrome has been reported at all ages. Often there is a prodrome of gastroenteritis or viral-like illness. Hemolytic-uremic syndrome has been seen in association with different infections, illnesses, and medications. It is a multisystemic disorder in which deposition of fibrin in the microvasculature leads to intravascular thrombosis. Although improvements in general patient care and dialysis have reduced the mortality rate from about 21% before 1974¹ to 4% to 7% by the mid-1980s,²⁻⁴ significant long-term morbidity still occurs in 10% to 20% of patients^{4,5} in the form of neurological sequelae, chronic renal failure, of hypertension. Several authors have emphasized the importance of neurological complications of

hemolytic-uremic syndrome, which occur in approximately 30% to 50% of patients.⁴⁻⁶ The present study examines the spectrum of neurological manifestations in patients with hemolytic-uremic syndrome. In a previous report, the relationship between laboratory parameters and outcome in hemolytic-uremic syndrome was detailed.⁷

Methods

Medical records of 78 children seen at the Children's Hospital, Boston, between 1976 and 1986 with the diagnosis of hemolytic-uremic syndrome were reviewed retrospectively. The age of these children ranged from 6 months to 16.5 years, with a mean of 4.8 years. Sixty-one of the 78 patients (78%) were 5 years of age or younger. Data were collected on presenting history, acute phase of illness, and outcome at hospital discharge. Cranial computed tomographic (CT) scans were reviewed by the authors (J.A.E. and R.S.) Laboratory values and urinary outputs were recorded and subsequently analyzed as previously described.⁷

Case Reports

Case 1

A previously healthy 11-month-old boy was admitted to a local hospital because of vomiting and diarrhea for four days. On admission, the hematocrit was 32%, platelet count 150,000/ μ L blood urea nitrogen 54 mg/dL, and creatinine 3.0 mg/dL. He was hydrated with intravenous fluids. He de-

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veloped bloody diarrhea and anuria. The child had generalized tonic-clonic seizures, which lasted approximately 20 minutes, prompting a transfer to the Children's Hospital. Upon arrival to the Children's Hospital, he was noted to be stuporous and had opisthotonic posturing, left abducens palsy, hypertonia, and bilateral Babinski reflexes. He continued to have frequent generalized tonic-clonic seizures with intermittent left-body partial motor seizures. He developed status epilepticus, requiring intubation and induction of pentobarbital coma. Other than a mild hyperkalemia (potassium, 5.5 mmol/L), the electrolytes were unremarkable. An initial cranial CT scan on the day of admission was considered to be normal. He was also treated with fresh frozen plasma and dialysis. On the second day, he remained comatose, although pentobarbital had been discontinued. On the third day, he became hypotensive and developed further brain stem dysfunction. Another CT scan revealed multiple areas of infarcts, particularly in the white matter. Multiple infarcts were seen also in the frontal and temporal cortical regions and the basal ganglia (Figure 1). An EEG at this time revealed diffuse slowing, right greater than left. Plasmapheresis was instituted, but shortly thereafter, he lost all brain stem reflexes. Fundoscopy revealed multiple retinal hemorrhages. Brain stem auditory evoked potentials were absent and an EEG showed no cerebral activity. Supportive care was withdrawn and the patient died.

Case 6

A 4-year-old girl was admitted to a local hospital with an 8-hour history of vomiting, bloody diarrhea, abdominal cramping, and diffuse abdominal pains. She had a low-grade fever of 101°F. At the other hospital, she was hydrated with normal saline. Her blood urea nitrogen was 154 mg/dL, creatinine 8.2 mg/dL, hematocrit 19%, and platelet 54,000/ μ L. The peripheral blood smear showed hemolysis (red blood cell fragments, helmets, and schistocytes). Her urine

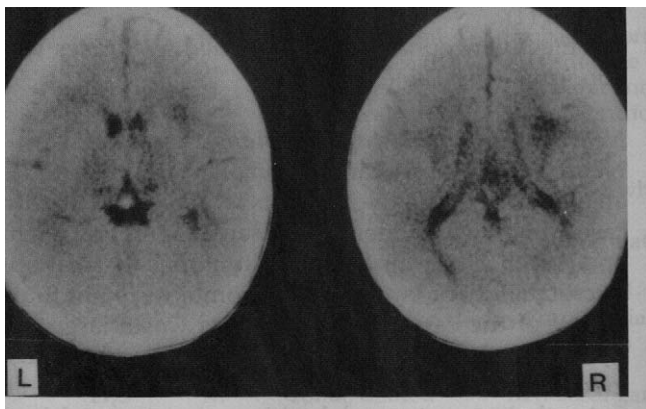


FIGURE 1
Cranial CT in case 1 showing multiple areas of low attenuation consistent with multiple infarcts, located in the white matter, frontal and temporal gray matter, and the basal ganglia.

output decreased gradually over a week, and she became anuric. She was transferred to the Children's Hospital, where peritoneal dialysis was started. After 3 days of uneventful dialysis, she was transferred back to the local hospital for further peritoneal dialysis. At transfer, the patient was edematous but had no neurological abnormalities. Her blood urea nitrogen was 33 mg/dL, and creatinine 4.2 mg/dL. Three days later the patient developed a fever, and her mental status declined. A lumbar puncture was performed and found to be normal. Blood cultures grew *Staphylococcus epidermidis*, and vancomycin was started. Over the ensuing 24 hours she developed a left hemiplegia, left facial weakness, and blindness. She was readmitted to the Children's Hospital, where she was noted to be irritable. Although her pupils were 4 to 5 mm in diameter and reacted to light bilaterally, she appeared to be blind. She had a left facial weakness and left hemiplegia with hyperreflexia and an extensor plantar response on the left side. ECG revealed left lateral wall ischemia, and echocardiogram confirmed left ventricular dysfunction. On the second hospital day, she became stuporous and developed papilledema and a dilated right pupil. She had a brief left-sided focal motor seizure. A CT scan revealed multiple areas of low attenuation, including a large right posterior frontal and left parieto-occipital lesions, consistent with multiple infarcts (Figure 2). Because of signs of increased intracranial pressure, she received dexamethasone and was intubated, paralyzed (with pancuronium), and hyperventilated. She received both peritoneal dialysis and plasmapheresis and had a gradual resolution of the anuria. On hospital day 15, she was successfully extubated but had a residual left hemiparesis and cortical blindness.

Case 9

An 11-year-old boy was admitted to a local hospital after a three-day history of abdominal pain, vomiting, and diarrhea. The diarrhea eventually became bloody. He was treated with promethazine and intravenous hydration. He developed microangiopathic changes on the peripheral blood smear and thrombocytopenia (platelet 49,000/ μ L). After three days of hospitalization, there was a decrease in urine output and transient alteration in mental status, prompting a transfer to the Children's Hospital.

On admission to the Children's Hospital, he was confused, frightened, and disoriented with poor short-term memory. There was a suggestion of bilateral abducens palsies. Deep tendon reflexes were increased and Babinski responses were present bilaterally. There was marked dysmetria and tremor. Laboratory studies revealed a hematocrit of 41%, a platelet count of 41,000/ μ L, blood urea nitrogen 53 mg/dL, and creatinine 3.2 mg/dL. His maximum blood pressure was 144 mm Hg systolic and 84 mm Hg diastolic. Hemodialysis was started, since previous appendectomy precluded peritoneal dialysis. An initial cranial CT scan was considered to be normal. Hemodialysis and plasmapheresis were initiated. On the second hospital day, he became comatose and had decerebrate posturing to painful stimuli. A repeat CT scan revealed a large left basal ganglia hemorrhagic infarct, right temporoparietal infarcts, and other multifocal areas of infarctions (Figure 3). Shortly thereafter the patient became acutely hypotensive and lost all brain stem reflexes. Despite supportive measures, he did not improve, and eventually brain death criteria were met and supportive measures were discontinued.

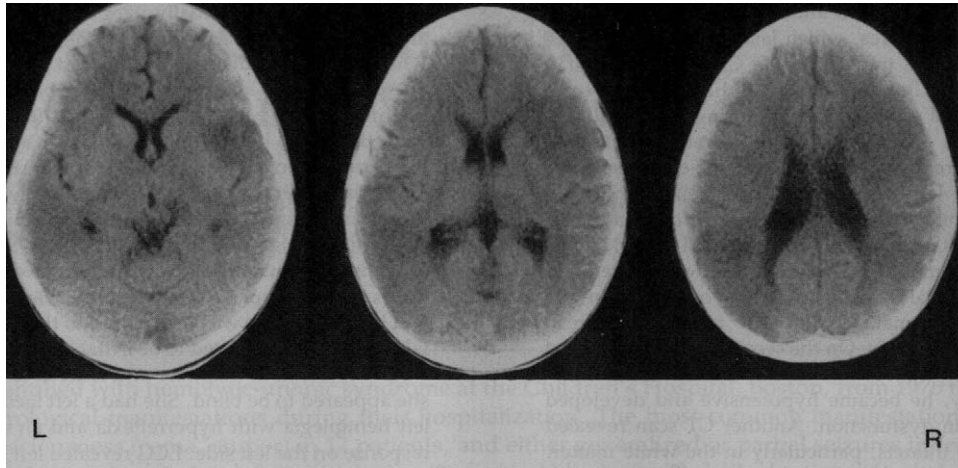


FIGURE 2
Cranial CT in case 6 showing multiple areas of low attenuation, large right posterior frontal and left parieto-occipital infarcts.

Results

Neurological Manifestations

Of the 78 patients with hemolytic-uremic syndrome, 16 (20.5%) had neurological manifestations during their hospitalization. Significant alteration in consciousness, ie, coma or stupor, was present in 12 patients. Seizures were also frequent and occurred in 10 patients (generalized in 5, partial in 3, and secondarily generalized in 2). Other manifestations included hemiplegia or hemiparesis (in 4 patients), decerebrate posturing (3), cortical blindness (2), hallucinations (1), and dystonic posturing (1).

Of the 16 patients with neurological manifestations, 11 (14.1% of all patients) had serious neurologi-

cal sequelae (Table 1). There were five deaths, and all occurred in children who had developed neurological complications. The remaining six children had persistent neurological signs at discharge, consisting of hemiparesis, altered level of consciousness, blindness, or dystonic posturing.

Five patients had transient neurological dysfunction (seizures, hallucinations, stupor, and hypotonia) but recovered completely, and at discharge had no evidence of neurological sequelae (Table 2).

Cranial CT was abnormal in eight of the 11 patients scanned. Findings are summarized in Tables 1 and 2. These abnormalities included: diffuse cerebral edema (in 4 patients), large vessel infarctions (3), multiple small infarcts (4), and parenchymal hemorrhages (1).

Electroencephalograms obtained in 8 cases were abnormal (see Tables 1 and 2).

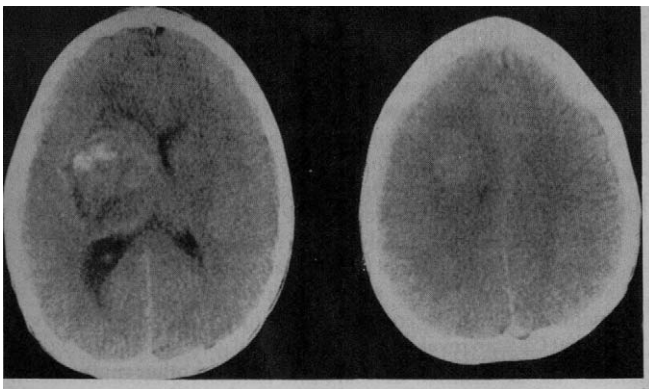


FIGURE 3
Cranial CT in case 9 revealing a large left basal ganglia hemorrhagic infarct, right temporoparietal infarct (at other levels), and multiple small areas of infarctions.

Neuropathological Manifestations

Neuropathological examination of the brain was available in three of the five patients who died. In all three cases, there was evidence of extensive cerebral edema and cerebellar tonsillar and tentorial herniations. Microthrombi or large vessel thrombi were not found in any of the cases. In case 9 there was a large confluent area of hemorrhagic infarction and necrosis involving the left basal ganglia, internal capsule, anterior thalamus, amygdala, hippocampus, and insular cortex (Figure 4). Left lateral ventricular hemorrhage was present with extension of the hemorrhage into the fourth ventricle. Another large (3 × 3 cm) cortical and subcortical hemorrhage was found in the

Hemolytic-Uremic Syndrome

TABLE 1
HUS Patients With Significant Neurological Sequelae

Pt	Age (yrs, mos)	Sex	Neurological Complications	CT	EEG	LP	Other Complications
1	0,11	M	Coma, seizures (generalized & focal, multiple)	Multiple infarcts, frontal temporal, basal ganglia	Background slowing, right > left	4 WBC, 400 RBC, glucose 81, protein 120	Death
2	2,1	M	Delirium, agitation, stupor, right hyperreflexia & Babinski signs, seizure	Normal			Diabetes, colectomy, pulmonary edema
3	2,2	M	Encephalopathy, myoclonus, left upper extremity dystonic posturing			1 WBC, 0 RBC, glucose 53, protein 26	Laparotomy (?perforation)
4	2,4	M	Coma, decerebrate posturing, seizures (generalized, multiple)		Marked voltage attenuation, left posterior region		Death
5	3,9	F	Coma, left hemiplegia, blindness	Right middle cerebral artery infarct, right hemispheric edema	Diffuse slowing, especially in right posterior quadrant		Death, rectal prolapse, gastrointestinal hemorrhage
6	4,2	F	Coma, left hemiplegia, seizure (focal), cortical blindness	Multiple infarcts, left occipital mass effect, right posterior frontal lesion			Myocardial infarction
7	4,5	M	Coma, bilateral Babinski signs, seizures (generalized & focal, multiple)	Probably normal, borderline subarachnoid and ventricular size	Diffuse slowing, suppression-burst pattern	Normal	Colectomy, varicella
8	5,1	M	Coma, papilledema, decerebrate posturing, seizures (generalized, multiple)	Poor gray-white matter differentiation (possible increased intracranial pressure)		0 WBC, 0 RBC, glucose 93, protein 10	Deep venous thrombosis
9	11,3	M	Coma, dilated and fixed pupils, right papilledema, decerebrate posturing	Left basal ganglia infarct/hemorrhage, right temporoparietal infarct, multiple low density areas, cerebral edema	Diffuse slowing, right > left		Death

(continued)

TABLE 1 (continued)

Pt	Age (yrs, mos)	Sex	Neurological Complications	CT	EEG	LP	Other Complications
10	14,7	M	Right hemiparesis, hyperreflexia, aphasia, seizures (focal, multiple)	Left cerebral infarct, bilateral cerebral edema			Colectomy, renal failure
11	15,4	F	Coma, seizures (focal, multiple)	Bilateral occipital infarcts	Left anterior focal discharges		Death

HUS = hemolytic uremic syndrome; LP = lumbar puncture.

TABLE 2
HUS Patients With Neurological Manifestation But Good Outcome

Pt	Age (yrs, mos)	Sex	Neurological Manifestations	CT	EEG	Other Complications
12	1,2	F	Seizure, hyperreflexia, bilateral Babinski responses, lethargy, irritability	Mild prominence of ventricles	Diffuse delta slowing	
13	2,2	F	Seizure			Respiratory arrest
14	3,2	M	Transient hypotonia, lethargy			
15	5,2	M	Hallucinations			Pleural effusion
16	14,10	F	Stupor, paresis of upward gaze	Bihemispheric swelling	Slow background, poor anterior-posterior gradient	

HUS = hemolytic uremic syndrome.

right parieto-occipital area. In addition, a small right occipital cortical hemorrhage and cervical and thoracic spinal cord petechial hemorrhage were noted. Thrombosis of the cerebral vasculature was not found. In case 1, there were multiple areas of irregular cortical softenings, particularly in the forebrain. Microscopic examination revealed widespread neuronal necrosis, consistent with anoxic encephalopathy. Case 11 revealed multiple areas of cortical necrosis predominantly in border-zone areas, right parieto-occipital hemorrhagic infarct, and pontine necrosis.

Discussion

In this study, we found a wide spectrum of neurological complications in patients with hemolytic-uremic syndrome, varying from generalized disturbances, such as stupor, coma, and seizures, to more focal

signs, including hemiplegia, hemiparesis, cortical blindness, and extrapyramidal signs. The incidence of neurological manifestations was 20.5% and the incidence of serious neurological sequelae was 14%. The incidence of serious neurological complications in other series varied from 30% to 50%.⁴⁻⁶ These differences may reflect either the improvement of intensive care in recent years or a bias in patient acquisition in our series.

Several mechanisms have been proposed to explain the neurological complications in hemolytic-uremic syndrome. Nonspecific metabolic derangements, hypertension, and renal failure, may in part account for the relatively high incidence of seizures and alterations in consciousness. Although intravascular coagulation and microthrombi are the hallmarks of this syndrome in the renal system, these have not been consistently found in the central nervous system.

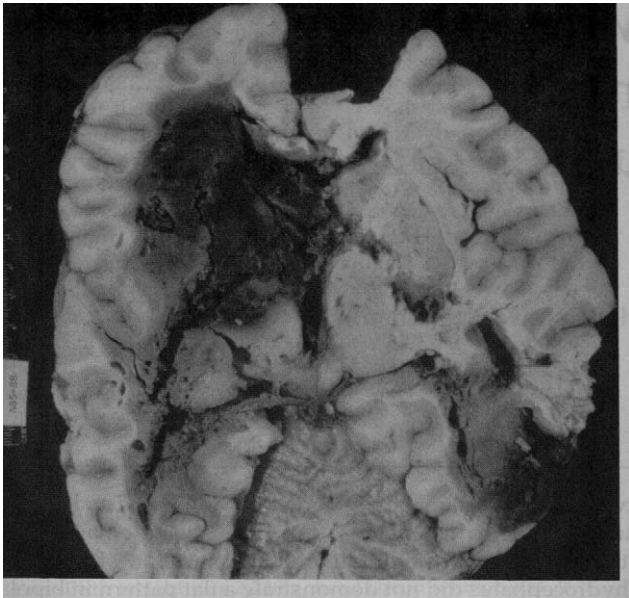


FIGURE 4
Gross pathology of the brain in case 9 with bilateral hemorrhagic infarctions and necrosis. Scattered fixation artifacts are present and have the appearance of multiple focal cystic lesions.

The three patients in our study who had neuropathological examination had evidence of focal ischemia in their brains. However, microthrombi and large vessel thrombi were not found. Rooney et al⁶ examined brains of seven patients who had neurological complications and died of hemolytic-uremic syndrome. In these cases, no microthrombi or distinctive pathological processes were found in the brains. In contrast, Upadhyaya et al⁸ studied the brains of three patients with hemolytic-uremic syndrome and severe neurological symptoms and found microthrombi in the brains of two cases. Evidence of ischemia with focal areas of infarction were noted in all three. Our series is somewhat unusual in that there were three patients who had large bland or hemorrhagic infarcts. Trevaathan et al⁹ recently reported three cases of hemolytic-uremic syndrome with large-vessel infarctions in the distribution of middle and anterior cerebral arteries as demonstrated by CT. Autopsy, available in one of the cases, revealed large-vessel thrombi in the cerebral

vasculature, while microthrombi were limited to the kidneys. Thus, in a few cases, the neurological complications may be caused by large vessel thrombosis, a process different from that responsible for the renal, hematological, and gastrointestinal manifestations.

There were five deaths in our series, all occurring in children who had neurological complications. It appears that the presence of neurological complications is a mortality risk factor. The mortality rate in hemolytic-uremic syndrome in our study (6.4%) is similar to those of more recent series.^{4,5}

In the past, the clinical usefulness of admission laboratory values to predict subsequent neurological dysfunction have been limited.³⁻⁵ As we reported previously, in this series the combination of serum calcium ≤ 7.6 mg/dL and urine output < 0.4 mL/kg/hr was able to predict serious morbidity or death with 82% sensitivity, 99% specificity, and 90% positive predictive value.⁷

Acknowledgment

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