Neuroradiologic Aspects of Pediatric Orthotopic Liver Transplantation

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To investigate the occurrence of neurologic symptomatology in pediatric orthotopic liver transplantation patients and to evaluate the utility of CT in uncovering the origin of their symptoms, we reviewed the medical records and head scans (when performed) of 71 patients. Neurologic problems occurred in 48%; the majority involved seizures, mental status changes, or coma. Patients who only had seizures generally had negative CT scans, except for two patients with minimal subarachnoid hemorrhages. Three-quarters of the comatose patients, however, had significant intracerebral hemorrhages defined by CT. Prominent sulci and ventricles were found in approximately one-third of the patients scanned, but did not correlate with symptomatology or steroid dose.

Once considered a heroic procedure, orthotopic liver transplantation (OLT) is becoming increasingly accepted as a method of therapy for a variety of primary and secondary disorders of the liver [1–5]. While the early experience with OLT had disappointingly high morbidity and mortality, recent experience has been encouraging. Owing mainly to better immunosuppressive techniques, especially the combination of cyclosporine and low-dose prednisone, OTL has shown improved survival statistics in the pediatric population [3, 4]. To date, only one article has specifically discussed neurologic problems of post-OLT pediatric patients [6]. To obtain a better understanding of this unusual group, and to investigate the utility of head CT scans in their evaluation, we reviewed our experience with 71 liver transplant patients at the Children's Hospital of Pittsburgh. Emphasis centers on the postoperative period; in particular, the correlation of neurologic symptomatology with findings on cranial CT.

Materials and Methods

The medical records of 71 patients who had liver transplant surgery at the Children's Hospital of Pittsburgh were reviewed. All patients underwent extensive preoperative evaluation [7], and each received one graft; approximately one-third had more than one grafting procedure. Ages ranged from 7 months to 18 years. The major indications for transplant surgery were biliary atresia or hypoplasia with previously failed drainage procedure (35 patients), metabolic diseases (22 patients), familial cholestasis (three patients), chronic hepatitis (four patients), cirrhosis (five patients), liver tumor (two patients).

Of the 71 patients, 27 had head CT scans; the majority of the scans were performed within the first 2 months after surgery. Most scans were performed without contrast enhancement. The scans were reviewed, and the findings were correlated with clinical symptomatology, as noted in the medical record.

Results

Thirty-seven (52%) of the patients had no significant postoperative neurologic symptomatology, and thus, had no head scans. Of the symptomatic patients, 17 had seizures, 10 had major mental status change or coma, two had prolonged

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encephalopathy, two had brain death, one had tremor, one had psychosis, and one had headache and visual impairment. Twenty-seven of these symptomatic patients had CT scans; seven patients had neurologic symptoms but were not scanned.

In the seizure group, two patients had subarachnoid hemorrhage visible on CT, one had probable white matter infarction, nine had enlarged sulci and ventricles (Fig. 1), and five had normal scans. Neither patient with subarachnoid hemorrhage had obvious AVM or aneurysm. Both were hypertensive at the time of their seizure; one had a relatively low platelet count (16,000–25,000/mm^3) but with normal clotting times. The hemorrhages were small, involving the perifalcine or peritentorial subarachnoid spaces, and caused no serious deterioration of the patient's course. The patient with infarct had focal frontal and parietal white matter lucencies of unclear origin (Fig. 2). The location of these lesions suggested infarcts in the arterial border zones; intraoperative hypotension was the suspected cause. The majority of remaining seizure episodes were seen in the early postoperative period and were attributed to hypertension [3, 4]. Other causes of seizure included metabolic abnormalities, medication, or combinations of these.

Four of the 10 patients with mental status changes became comatose. Of these, three had intracranial hemorrhages; one of these had subdural and parenchymal hematomas with subarachnoid hemorrhage (Fig. 3), another had an isolated subdural hematoma (Fig. 4), and the third had a large intracerebral hematoma (Fig. 5). All three of these patients had coagulopathies. Two had hypotensive episodes associated with the bleeds; none was hypertensive. These hemorrhages all presented as acute events and resulted in death in a short period of time.

In the group of patients having mental status changes without coma, one had CT evidence of infarct, three had enlarged sulci and ventricles, and two were normal. The infarct was thought to be a possible result of an air embolus at the time of surgery [6]. In other cases, mental status change was attributed to metabolic causes (e.g., hyponatremia, hepatic encephalopathy), sepsis, or hypotension.

Patients with posttransplantation tremor or psychosis had normal cerebral CT except for evidence of volume loss. The single patient complaining of headache had very small ventricles and was thought to have pseudotumor cerebri, probably related to steroids. One patient was scanned for encephalopathy, which persisted for 2 weeks after transplant. This patient had Wilson disease, with typical lucencies of the basal ganglia. Over the next 4 months, he became neurologically normal and repeat CT scans showed resolution of the basal ganglia lucencies. (This patient is described in more extensive detail in another article [8].) One patient was examined for brain death resulting from intraoperative hypoperfusion. CT revealed diffuse brain swelling and an absence of vascular opacification at the circle of Willis after IV bolus of contrast material, supporting the clinical impression of brain death [9].

Only three patients had preoperative CT scans, indicated

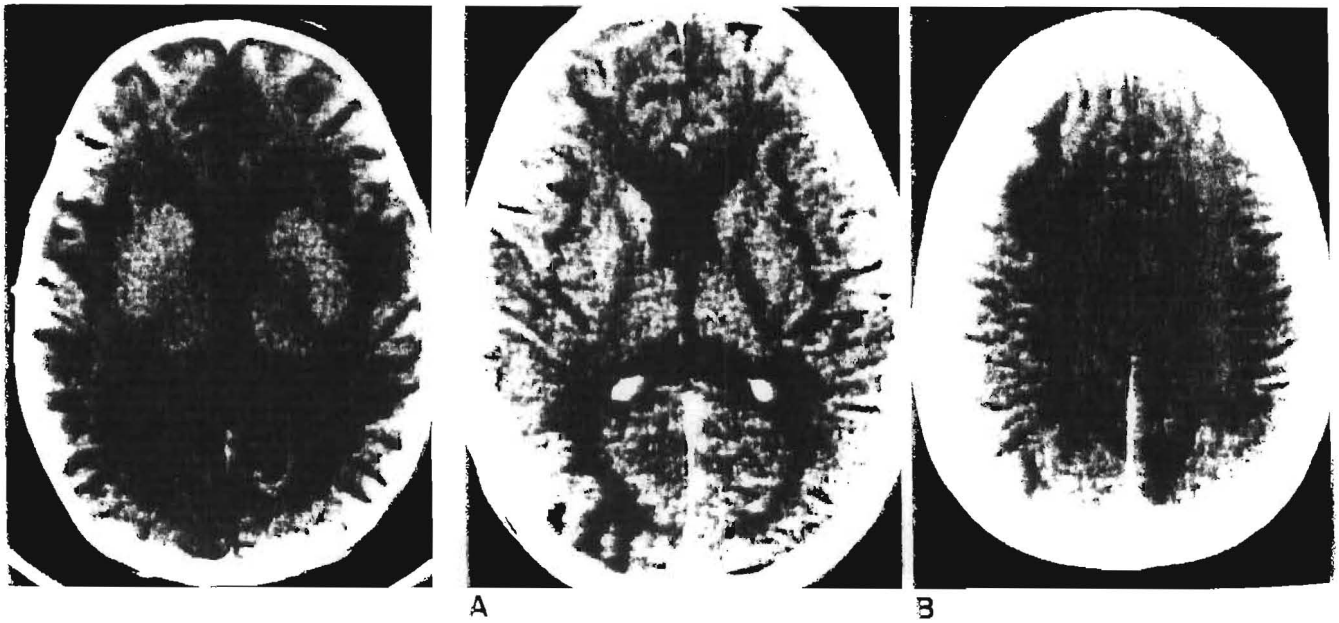

Fig. 1.—3-year-old boy with biliary atresia and three previous orthotopic liver transplants whose course was complicated by infarction of first two transplanted livers and a myocardial infarction. He had transient episodes of eye deviation thought to represent seizure activity. Unenhanced CT scan shows enlargement of ventricles and sulci.

Fig. 2.—10-year-old boy with liver failure secondary to hepatitis of unknown origin. Focal seizures involving the left hand 11 days after second liver transplant prompted CT.
A, Enhanced CT scan shows abnormal lucency (infarct) in right occipital white matter.
B, Higher section shows similar lucencies in right frontal and bilateral parietal white matter.

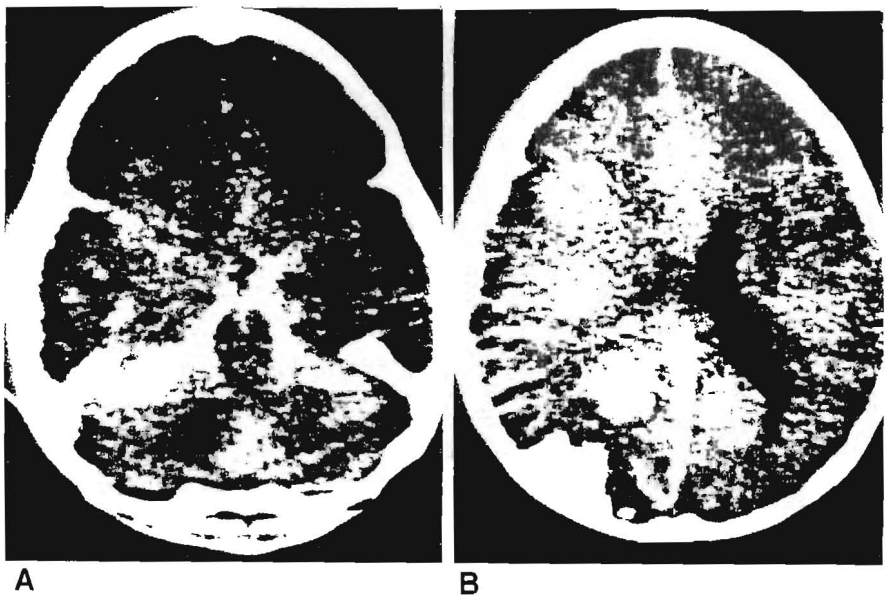

Fig. 3.—8-year-old girl with hepatic failure due to biliary obstruction after repair of a choledocal cyst. 1 hr after waking from her second transplant she became hypotensive and then comatose.

A, Unenhanced axial CT scan at level of midbrain shows massive subarachnoid hemorrhage.

B, Higher section shows intraparenchymal, subarachnoid, and subdural hemorrhage, confirmed at postmortem examination.

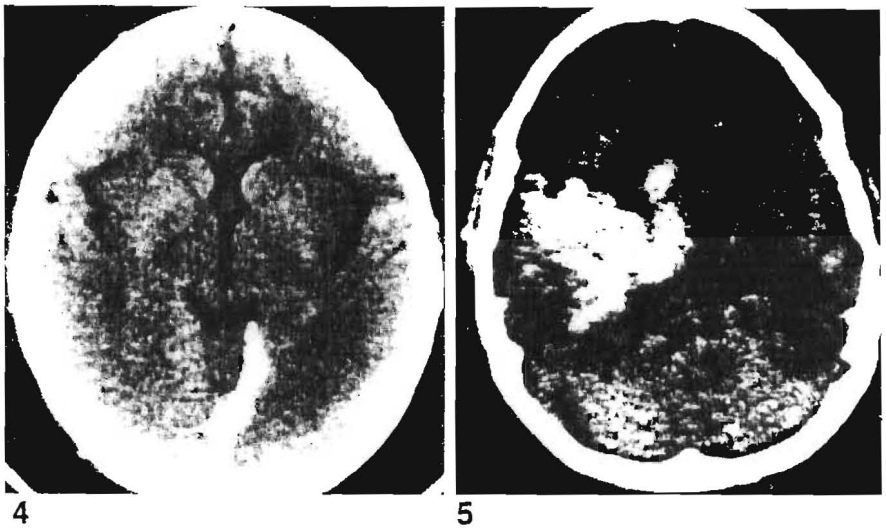

Fig. 4.—4-year-old with biliary atresia and situs inversus who received auxiliary liver transplantation. 4 days after the second transplant the patient went into cardiac arrest, was resuscitated, but remained comatose. CT scan shows relatively small subdural hematoma along tentorium, which extended upward along posterior falx on higher section (not shown).

Fig. 5.—19-year-old with hepatic failure due to alpha-1-antitrypsin deficiency. 4 weeks after his third transplant, he suddenly became unresponsive. CT scan shows massive right basal ganglionic area hemorrhage.

by a previous seizure disorder. Two of these had prominent ventricles and sulci; the other was normal.

Autopsy correlation of the 71 patients was limited. Only two patients, one with diffuse brain edema and herniation, the other with massive cerebral hematoma, had been evaluated with CT near the time of death. Cerebral findings in the seven other patients with neurologic autopsy included two patients with brain abscesses (Candida and Staphylococcus) from systemic sepsis, one with Aspergillus vasculitis, one with disseminated cortical Candida, one with subarachnoid hemorrhage, one with sagittal sinus thrombosis, and one with diffuse edema.

Prominence of ventricles and sulci was the most common CT finding, occurring in 15 of the 28 patients who were scanned. There was no correlation of "atrophy" on CT with steroid or cyclosporine dose or duration of therapy. Although patients who had been on long-term immunosuppression usually had marked enlargement of sulci and ventricles, some patients showed similar changes early in their course of therapy.

Discussion

Liver transplantation in pediatric patients has an attendant array of possible medical and surgical problems. Among the more common early postoperative complications are hypertension, acute transplant rejection, infection (viral, fungal, or bacterial), pulmonary edema, transplant vascular thrombosis, and biliary leakage. Later complications include chronic transplant rejection, renal dysfunction, sepsis, biliary and vascular strictures, immunodefensive compromise, and lymphoproliferative disorders [1–5]. Clearly, the potential for infectious, metabolic, hematologic, or ischemic insult to the CNS is great.

Yet, little emphasis has been placed on neurologic problems in this patient population.

Neurologic symptomatology occurred in about half of our patients but was relatively benign in most instances. Seizure represented the most frequent problem, occurring most commonly in the early postoperative period. The majority of seizures were related to hypertensive episodes, without evidence of intracranial bleeding. Such hypertensive seizures have been attributed to vascular spasm or breakdown of autoregulation of cerebral blood flow with resultant ischemia and/or edema [10]. In only two patients were seizures associated with spontaneous subarachnoid hemorrhage. In each instance, the hemorrhage was small and ran an uneventful course.

Coma represented a less common but distinctly more serious neurologic problem. Three of the four comatose patients had significant intracranial hemorrhage, including subarachnoid, subdural, and intraparenchymal locations. In contrast to the patients with seizures, these patients presented with acute hypotensive rather than hypertensive episodes; they all had rapidly deteriorating courses. All these patients had coagulopathies involving platelets and/or coagulation factors that predisposed them to spontaneous hemorrhage. Patients with less severe mental status change (e.g., confusion or lethargy not progressing to coma) did not have CT evidence of intracranial bleeding.

Our cases of perioperative brain death and cerebral embolism emphasize the complex nature of liver transplantation surgery. During removal of the diseased liver and placement of the orthotopic liver, major arteries and veins must be cross-clamped and bypassed [1, 2, 5]. Potentially dangerous vascular compromise, thrombosis, and hypotension can occur, especially if vascular anomalies are present [4]. Perioperative air embolism to the cerebral circulation represents another potential insult to the brain from liver transplantation. Recognized mainly in the adult transplant population, it results from air entering the venous system and crossing pulmonary arteriovenous shunts to enter the left heart. These shunts are thought to represent normal anastomotic pulmonary arteriolevenule connections that are enlarged in the context of chronic liver disease [6].

Infections are common during the postoperative transplantation period, due primarily to immune suppression [1–5]. However, in none of our patients were CNS infections manifest on CT done at the time of original neurologic symptomatology. More liberal use of IV contrast material would improve detection of CNS infections, but this benefit must be weighed against contrast nephrotoxicity in these patients, who often have renal impairment at the time of the examination. Our limited autopsy series indicates that when the CNS was involved by infection, it was as part of a terminal event with disseminated bacteria or fungi. Such findings are in keeping with other transplant populations (e.g., renal transplantation) in which infections in non-CNS locations more commonly lead to septic complications [11].

A large number of our patients (just over half those scanned) had prominent ventricles and sulci on CT, which is often erroneously thought to represent "atrophy." There was no definite single etiology for this appearance. Specifically, the use of steroids, which is a known cause of enlarged sulci and ventricles on CT [12], could not explain all of our observations. We found no correlation between CT "atrophy" and dose or duration of steroid treatment. In fact, because of the use of cyclosporine, steroid doses were often quite low. Most certainly the cause of ventricular and sulcal enlargement is multifactorial. Other medications, such as diuretics, antihypertensives, anticonvulsants, and antibiotics, may have indirect effects that add to those of immunosuppressants. So, too, the generalized catabolic state resulting from chronic liver disease and immunosuppression may result in loss of brain volume, similar to the reversible volume loss described in patients with anorexia nervosa and Cushing syndrome [13].

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