Acute Neurological Complications After Liver Transplantation with Particular Reference to Intraoperative Cerebral Air Embolus

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Nine of 48 adult patients who underwent orthotopic liver transplantation developed significant clinical neurological abnormalities recognized shortly after operation. Decrease in consciousness occurred with resultant coma, focal and generalized seizures and the occasional appearance of a state of akinetic mutism. Neuropathological abnormalities consisted of multifocal areas of infarction in cerebral cortex and basal ganglia in five patients, central pontine myelinolysis in five (often more extensive than usually reported), Wernicke's encephalopathy in three, glial nodules in two, and fungal abscesses in one. Alzheimer II astrocytosis was found in all brains available for retrospective study. There was direct evidence in two of the patients that air embolization from the homografts had occurred. Correlation of this with the brain infarcts in these and other cases seems reasonable. The ease with which air passed to the systemic circulation is explicable by the right to left venous–arterial shunts that are common in chronic liver disease. With the delineation of this cause for the neurologic complications, measures to prevent it in future cases have been described.

AMONG ADULT RECIPIENTS of orthotopic liver homografts, a high incidence of acute and profound neurologic disability has been recognized shortly after operation.[21] We report here a brief clinical–neuropathological survey of these central nervous system complications. Particular emphasis will be placed on the possible etiologic role, in some instances, of air emboli originating from the hepatic homograft, and on the avoidance of such emboli in future cases.

Case Material

Forty-eight adult patients, aged 19–68 years, [...] treated between March, 1963 and April, 1976. [...] surgical and postoperative management techni[...] have undergone modifications during this time, [...] but these will not be described since the nervous sy[...] complications occurred throughout the 13 year [...] perience. Within the group of 48 adults, nine pat[...] sustained clinically significant neurological dam[...] during or soon after operation. In the meanw[...] 60 pediatric recipients, ages one to 18 years, w[...] treated in a manner similar to the adults with[...] comparable complications.

Some clinical features of the 9 cases are li[...] in Table 1. The patients were 31–52 years old. [...] had end-stage cirrhosis and evidence of portal hyp[...] tension. Three were alert just prior to operation. T[...] other six had evidence of altered consciousn[...] ranging between confusion and coma.

Postoperatively, all nine patients died. Their neu[...] logic disability during the three to 72 days of po[...] transplantation survival was correlated with the qua[...] of liver function obtained from the homograft a[...] with neuropathologic observations at autopsy. T[...] possible contributions of coagulation disorders ([...] pecially thrombocytopenia), hyperosmolarity sta[...] hyponatremia and other metabolic abnormalities w[...] examined by chart review. Anesthesia records w[...] searched for other factors which might have c[...] tributed to the central nervous system events.

TABLE 1. *Findings Before and After Operation**

Date of Opera-tion	Postoperative Survival (Days)	Preoperative State of Consciousness	Postoperative Lucid Interval	Initial Neurologic Complication	Further Neurologic Complications
7/16/63	6	Awake	1 day	Seizures	Coma
1/16/70	3	Awake	8 hours	Focal seizure	Coma
10/8/70	26	Comatose	None	Focal seizure	Coma
12/22/70	32	Awake	1 day	Leg spasticity	Extensor spasm of legs; Akinetic mutism
11/22/72	41	Comatose	3 days	Decreased mentation	Right hemiparesis: Akinetic mutism
10/7/73	22	Confused	20 hours	Seizures	Stupor
2/8/75	72	Stuporous	36 hours	Sudden coma	Seizures: coma
3/28/76	22	Confused	None; ?awake but immobile	Seizures	Coma: akinetic mutism
4/5/76	17	Comatose	None	Seizures	Right hemiparesis

* The average age was 41.9 ± 6.2 (S.D.) years, range 31 to 52. Patients OT 4, 32, 39 had alcoholic cirrhosis and the others had post necrotic cirrhosis.

Results

Clinical Observations

Each of the transplant operations was exceptionally difficult technically and often required a large quantity of blood replacement which ranged from 1,500 to 2,500 ml averaging 10,300 ± 6,900 (S.D.) ml (Table 1). Serum hyperosmolarity was observed in only two cases. There was not a consistent pattern of hyper- or hyponatremia, hyperkalemia, pH disequilibrium, or hyperglycemia during the operations or during the first 72 hours afterwards.

Postoperatively, six of the nine patients had a distinct lucid interval which lasted from a few hours to three days (Table 1). With the onset of the neurological disability, often ushered in by focal or generalized seizures or both, there was a sudden or gradual decrease in consciousness. At times, a few patients (OT 40, 60, 107) seemed to regard their environment without responding to it, much as though they were in a vegetative state (akinetic mutism). Fluctuation in the level of consciousness from one day to the next or from hour to hour was common. Although a few patients (Table 1) appeared to have focal signs, most did not. This observation, together with the usual appearance of a diffusely slow and nonfocal electroencephalogram, gave support to the clinical impression of a diffuse toxic or metabolic encephalopathy.

During the life of these patients, however, clear identification of what the causative factors for such an encephalopathy might be could not be made. Standard liver function tests usually were not very abnormal and in six of the nine cases were totally or almost completely normal. There was no evidence in any pa-

tient of early post-transplantation liver necrosis. Although cerebral angiography in one patient (OT 60) suggested thrombotic or embolic disease, most coagulation factors in this and other patients, as exemplified by the prothrombin times which ranged from 20% to 100% were only moderately subnormal. Thrombocyte counts were generally depressed during and after operation. The lowest platelet counts in the 9 cases averaged 71,000 ± 53,000(S.D.)/mm³ intra-operative and 34,000 ± 19,300 (S.D.)/mm³ postoperative.

Pathological Observations

As has been reported before,[21] the transplanted livers contained little or no evidence of rejection, despite the fact that aggressive immunosuppressive therapy had been discontinued in some of the recipients for as long as several weeks. Two of the nine homografts were completely normal.

The neuropathological findings in eight brains personally surveyed by one of us (SAS) are summarized in Table 2. Multiple focal areas of frank infarction or ischemic change were noted in five of the eight brains. Most of these were in the cerebral cortex or basal ganglia, and were usually small to moderate in size. However, in one patient (OT 60), the cortical and ganglionic infarction was widespread.

Central pontine myelinolysis was found in five brains (Table 2) and varied from scattered foci of demyelination to a very widespread confluent lesion in the basis pontis. In all five patients demyelination of pathways within the basal ganglia was noted and in four (OT 40, 60, 72, 107) there was some degree of extension of the demyelination into the pontine tegmentum.

Typical changes of Wernicke's encephalopathy were

TABLE 2. *Neuropathological Abnormalities*

OT No.	Alzheimer II Glia	Central Pontine Myelinolysis	Basal Ganglia Demyelination	Pontine Tegmental Demyelination	Infarction or Ischemia	Wernicke's Encephalopathy	Glial Nodules	Fungal Abscess
4*	–	–	–	–	–	–	–	
32	+	–	–	–	–	–	+	
39	+	–	–	–	+	–	–	
40	+	+	+	+	+	–	–	
60	+	+	+	+	+	–	–	
72	+	+	+	+	+	+	–	
97	+	+	+	–	–	+	+	
107	+	+	+	+	+	+	–	
108	+	–	–	–	–	–	–	

* Tissues not available for retrospective examination.

noted in the mamillary bodies of 3 patients (OT 72, 97, 107). Alzheimer Type II astrocytosis was widespread and profound in amount in all eight brains available for reexamination. In two (OT 32, 97) glial nodules like those described in kidney transplant recipients with disseminated cytomegalovirus infection[14] were discovered in the pontine tegmentum. Fungal abscesses were located in the frontal lobes and in the cerebellum of patient OT 97. This recipient had disseminated candidiasis.

Direct Evidence of Air Embolism

Air embolism during operation was observed in some of the first orthotopic liver recipients, including one who developed bilateral partial leg paralysis (see Reference 20, p. 151). It was thought that this patient might have had a patent foramen ovale to explain this passage of the air to the systemic circulation, but a septal defect was not present at autopsy 143 days later. The upward passage of air was verified in this patient and in others who did not have neurologic findings by aspiration of air from a right atrial catheter. The source of this air was thought to have been from small tributaries of the vena cava near the diaphragm, rather than from the graft itself.

In the nine patients in the present report, a systematic search for signs of air emboli was not made at the time of their neurological deterioration or at the subsequent autopsies. However, air embolism was definitely implicated in two of the nine cases.

After transplantation, patient OT 32 awakened promptly and was completely normal for several hours. He then suddenly had a focal seizure, never regained consciousness, and died two and one-half days later. At autopsy, the cavernous sinus and several cerebral arteries contained gross air. To explain these puzzling findings, the prosector initially speculated that the air might have been introduced artefactually during the postmortem removal of the calvarium, but in retrospect this seems unlikely.

Immediately after revascularization of the graft, patient OT 107 had a cardiac arrest which she was promptly resuscitated. Air was drawn from a right atrial catheter immediately ward. It was feared that she might be dead intraoperatively but afterwards this was nized not to be the case. During her 22 operative days of life, she remained unrespon and had multifocal seizures. Autopsy disclosed areas of infarction in the cerebral cortex and putam central pontine myelinolysis, degeneration of white ter pathways within the putamen, Wernicke's cephalopathy and mild diffuse Alzheimer II astroc throughout the brain.

At about the same time as the death of OT 107, research on the preservation of canine homografts was being conducted in our labor After orthotopic transplantation, significant of air were recovered from the right atri ventricle and even from the coronary sinus in of the dogs which died immediately after the proce We then suspected seriously that the same thing occurred in our patients, but with passage of the to the left heart via the abnormal vascular ch that are present in liver disease (see Discussion).

The Prevention of Air Embolism

Since April, 1976, the technique shown in Figure has been used during all human liver transplantation. The portal perfusion that is used to chill the o is continued as the upper and lower vena ca anastomoses are performed, care being taken to out any residual bubbles as the anastomoses are c pleted. The portal venous and hepatic arte anastomoses are then performed in the usual With revascularization, after completion of either or all four anastomoses, the anesthesiologist listened with the esophageal stethoscope for a tory evidence of air embolization. None has been tected since the use of this technique. Furthermo no neurologic complications have been encountered

...4 adults and nine children so treated since 1976.

Discussion

...our adult patients, cerebral air embolism, de-...from residual air in the homograft vena cava or ...ic veins, is suspected to have been responsible ...least some of the neurological complica-...documented in almost 20% of our adult liver ...ients. Appreciation of this concept has been slow ...has been delayed by an imprecise understanding ...ow air could regularly bypass the lung, go to the ...heart and systemic circulation and then to the ...

...actuality, the ability of air to readily cross the ...barrier is understandable. Even in normal human ..., potential connections exist between the pul-...ry artery and venules.[12,18,23] These anastomotic ...els become patent under various conditions and ...cularly with chronic liver disease. Using physio-... or anatomic techniques of study, large right-to-...arteriovenous (A-V) shunts have been well docu-...ed within the lung or on the lung surface of ...ts with hepatic ailments.[1,2,5,13] In addition, com-...tions may exist between the portal and azygos ... In the postmortem study of a patient who ...of Laennec's cirrhosis, Calabresi and Abel-...[4] injected a plastic mass into the portal vein ... recovered part of it from the pulmonary vein ...left atrium. Thus, it appears reasonable to believe ... air could easily make its way by any one of ...ral routes to the systemic circulation and lodge ...in the central nervous system, producing focal ...age.

As has been summarized by Kennedy et al.[7] and ...ng,[24] additional factors must also be considered in ...er to understand the clinical features of air ...olism. For example, the location of air embolus ...estration may influence the rate at which the air ...sorbed. If air makes its way to the right ...t or pulmonary arterial circulation and is thus ...osed to unsaturated hemoglobin, oxygen and car-...dioxide are absorbed many times more rapidly than ...e air is sequestered in the pulmonary veins or ...heart where there is highly saturated hemoglobin. ..., in patients with the right-to-left shunts of liver ...ase, air presumably could quickly bypass the ..., enter the pulmonary veins and left heart and by ...ging in these latter locations could remain a threat ...the brain and other organs for many hours or even ...

The fact that air bubbles may persist for a long time ...fore a final movement to the brain could explain ...lucid interval in some of our patients before the on-...et of seizures, paralysis and coma. Kindwal[8] and
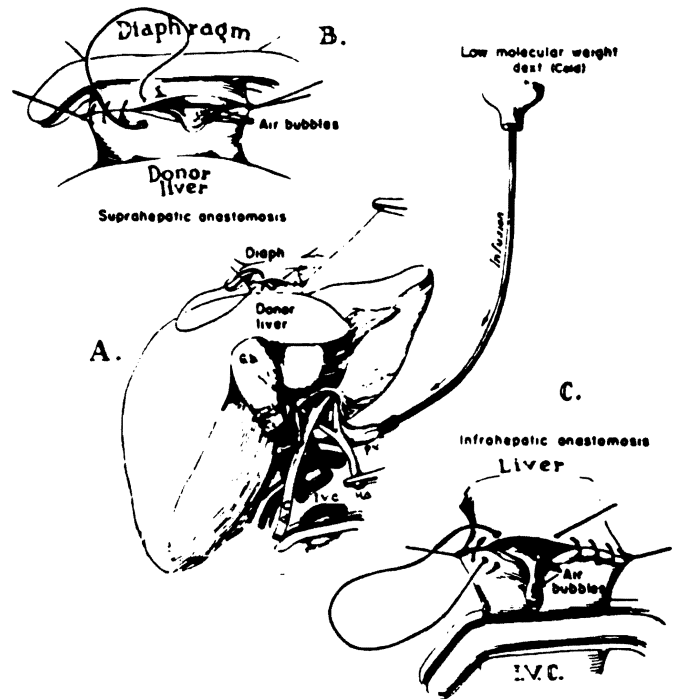

FIG. 1. Technique to prevent air embolism from orthotopic liver homografts. A. Continuous perfusion of solution through portal vein as vena caval anastomoses are constructed. B. C. Escape of air bubbles as the anastomoses are completed.

Thomas and Stephens[22] have referred to similar delays in patients whose recovery from open heart surgery or chest trauma was complicated by air emboli which were thought to have originated in the lungs or left heart.

The gases used for anesthesia can also affect the outcome. If nitrous oxide is being used at the time of air embolism, the volume of the air bubble is increased by diffusion into it of nitrous oxide.[10,11] Thus, this agent should be avoided or discontinued whenever air embolism is a possibility.

The sparing of infants and children may have occurred because air trapping was proportionately less in their smaller and more compliant livers, or because the right to left venous anastomoses were not so well developed in these younger recipients with liver disease as in the adults. In any event, the infusion technique now being used during liver transplantation apparently has eliminated the source of air emboli in the high risk adult patients.

The neuropathological correlate of the presumed cerebral air embolization is most likely the focal, and occasionally extensive, ischemic infarction seen best in the cerebral cortex and corpus striatum. However, air embolization may have been only one of multiple factors in the sudden development of the neurologic complications. Preexisting damage to the central nervous system could have played a primary or secondary etiologic role. An association between

advanced liver disease and brain changes has been well known since the classical description by Höesslin and Alzheimer in 1912[6] of hypertrophy of astrocytes with liver failure similar to that seen in the brains of our patients. Many other morphologic abnormalities have been described in the intervening years.[16,19]

Of particular interest has been the association of cirrhosis and central pontine myelinolysis.[17] A specific etiology for this latter condition has not been defined, although severe malnutrition[15] and hyponatremia[3] have been suggested. Only one of our patients was transiently hyponatremic. Severe malnutrition has also been correlated with Wernicke's encephalopathy, found in a third of our patients. Hence, thiamine replacement therapy may be highly indicated in potential liver recipients.

The degree of degenerative changes has been severe in the brains of many of our liver recipients, including the majority of those in this report. These abnormalities, including a consideration of their possible antemortem diagnosis, will be the subject of a separate publication.

Eventually, other hazards associated with liver transplantation may be found to contribute to the neurologic complications. In an earlier publication,[21] it was speculated that hemorrhage caused by thrombocytopenia, which was invariably present, or by other abnormal clotting factors could have occurred into areas of pre-existing brain degeneration. No neuropathologic support for this hypothesis could be uncovered in the present study.

Hyperosmolarity syndromes have not been a consistent problem in our experience, although excessively high blood sugars have been suggested by Lampe, Simmons and Najarian to explain the severe neurologic damage in one of their juvenile liver recipients.[9]

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