

Successful Use of Alternate Waste Nitrogen Agents and Hemodialysis in a Patient With Hyperammonemic Coma After Heart-Lung Transplantation

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Background: Lethal hyperammonemic coma has been reported in 2 adults after lung transplantation. It was associated with a massive elevation of brain glutamine levels, while plasma glutamine levels were normal or only slightly elevated. In liver tissue, glutamine synthetase activity was markedly reduced, and the histologic findings resembled those of Reye syndrome. The adequacy of therapy commonly used for inherited disorders of the urea cycle has not been adequately evaluated in patients with this form of secondary hyperammonemia.

Objective: To determine whether hemodialysis, in conjunction with intravenous sodium phenylacetate, sodium benzoate, and arginine hydrochloride therapy, would be efficacious in a patient with hyperammonemic coma after solid-organ transplantation.

Design: Case report.

Setting: A children's hospital.

Patient: A 41-year-old woman with congenital heart disease developed a hyperammonemic coma with brain edema 19 days after undergoing a combined heart and lung transplantation.

Methods: Ammonium was measured in plasma. Amino acids were quantitated in plasma and cerebrospinal fluid

by column chromatography. The effectiveness of therapy was assessed by measuring plasma ammonium levels and intracranial pressure and performing sequential neurological examinations.

Results: The patient had the anomalous combination of increased cerebrospinal fluid and decreased plasma glutamine levels. To our knowledge, she is the first patient with this complication after solid-organ transplantation to survive after combined therapy with sodium phenylacetate, sodium benzoate, arginine hydrochloride, and hemodialysis. Complications of the acute coma included focal motor seizures, which were controlled with carbamazepine, and difficulty with short-term memory.

Conclusions: The aggressive use of hemodialysis in conjunction with intravenous sodium phenylacetate, sodium benzoate, and arginine hydrochloride therapy may allow survival in patients after solid-organ transplantation. An acute acquired derangement in extra-central nervous system glutamine metabolism may play a role in the production of hyperammonemia in this illness that resembles Reye syndrome, and, as in other hyperammonemic disorders, the duration and degree of elevation of brain glutamine levels may be the important determining factors in responsiveness to therapy.

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HYPERAMMONEMIC COMA with brain edema is now recognized as a complication of solid-organ transplantation as well as of bone marrow transplantation and chemotherapy for cancer.¹⁻⁸ It was the cause of death in 2 of our patients after lung transplantation.^{1,2} Normal or mildly abnormal liver-associated laboratory test results accompanied the hyperammonemic coma in these 2 adults. Histologic examination of the liver in 1 of the patients revealed severe microvesicular steatosis and accumulation of mitochondrial crystalline structures within hepatocytes, find-

ings comparable to those previously reported in patients with Reye syndrome.^{1,2} Potential etiologic factors include the use of immunosuppressive agents and parenteral nutrition in the patient undergoing severe stress.²

The cause of death in the patients with hyperammonemic coma after lung transplantation was increased intracranial pressure (ICP) due to brain edema. Yet, while the ultimate cause was attributed to hyperammonemia, the plasma amino acid levels in these 2 patients were somewhat anomalous in that the levels of glutamine, the most prevalent amino acid in plasma in man and the one that best re-

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flects the whole-body waste nitrogen burden in hyperammonemic states in infants and children with congenital urea cycle enzyme defects,⁹ were either inappropriately normal or only slightly increased in concentration. This phenomenon had been noted in other patients with secondary hyperammonemia in the setting of bone marrow transplantation and chemotherapy.⁶ To gain insight into the biochemical mechanisms underlying this effect, hepatic glutamine synthetase (GS) activity was assayed in the 2 patients, and a marked reduction in activity and levels of GS protein was detected.² This reduction suggested that a secondary acquired hepatic GS deficiency may play a role in the pathogenesis of hyperammonemic coma after organ transplantation, perhaps by allowing more waste nitrogen to circulate as NH_4^+ rather than as glutamine. Does this mean that these patients with hyperammonemic encephalopathy fail to accumulate glutamine within the brain? The answer is no, since 1 of our patients had an enormously elevated level of glutamine in cerebrospinal fluid (CSF).² In fact, these anomalous findings serve to underscore the critical role of glutamine in brain edema.⁹

Dialysis therapy has not proved effective for treating this type of secondary hyperammonemia.² In primary hyperammonemia due to urea cycle enzyme defects, sodium benzoate and sodium phenylacetate are extremely beneficial in lowering plasma NH_4^+ levels and the whole-body waste nitrogen burden when they are used in conjunction with arginine to prevent amino acid deficiency or to stimulate synthesis of urea cycle intermediates for urinary excretion.⁹ Also, the successful employment of sodium benzoate and/or sodium phenylacetate for the treatment of hyperammonemia with high-dose chemotherapy and portosystemic encephalopathy has been reported.⁵ Whether optimal use of these alternate waste nitrogen agents,⁹ as well as hemodialysis, would be efficacious for the patient with hyperammonemia after solid-organ transplantation was unknown. We report the first successful use (to our knowledge) of these combined modalities in a woman with hyperammonemia and normal plasma glutamine levels with brain edema and elevated CSF glutamine concentrations following a combined heart-lung transplantation.

REPORT OF A CASE

A 41-year-old woman with Ellis-van Creveld syndrome (Online Mendelian Inheritance in Man, 22550¹⁰) underwent combined heart and lung transplantation because of severe fixed pulmonary hypertension and congestive heart failure secondary to congenital common atrium and left cardiac hypoplasia. Preoperatively, she demonstrated signs and symptoms of end-stage pulmonary vascular disease and congestive heart failure, including anasarca, severe debilitation, and functional limitation (New York Heart Association class IV). Her medications included digoxin, furosemide, spironolactone (Aldactone), ranitidine, potassium chloride, dopamine, nifedipine, and lidocaine. Postoperatively, she was treated with cyclosporine, azathioprine, methylprednisone sodium succinate (Solu-Medrol), fentanyl citrate, isoproterenol, spironolactone, furosemide, ranitidine, cefazolin sodium (Ancef), nystatin, and gan-

cyclovir. On postoperative day 4, treatment with cyclosporine and azathioprine was discontinued and tacrolimus and mycophenolate mofetil were added to the regimen. The patient received total parenteral nutrition with 1 g of amino acids per kilogram of body weight per day. Function of her transplanted organs was consistently good, with hyperdynamic ventricular performance, a clear chest x-ray film, and adequate oxygenation and ventilation with minimal ventilatory support. However, as expected, owing to the thoracic abnormalities associated with Ellis-van Creveld syndrome and her severe debilitation, she required prolonged mechanical ventilatory support. A tracheostomy was placed on postoperative day 12. Almost immediately after the transplantation, progressive renal failure developed, with concordant increases in both serum urea nitrogen and creatinine levels, in association with cyclosporine and tacrolimus levels that were in the low therapeutic range, and normal liver-associated laboratory test results. On postoperative day 5, all calcineurin inhibitors were withheld owing to renal failure; treatment with mycophenolate mofetil was discontinued and azathioprine was again added to the regimen. On postoperative day 18, fever and leukopenia developed; cultures (the results of which were subsequently negative) were obtained and empiric antibiotic therapy was begun.

On postoperative day 19, the patient displayed altered mental status followed by the rapid development of myoclonus, seizures, and coma. An electroencephalogram showed bilateral slowing, disorganized background activity, and triphasic waves over both frontal regions. Clonazepam therapy was instituted. A computed tomogram of the head showed no evidence of bleeding or edema. A plasma ammonium (NH_4^+) level was 257 $\mu\text{mol/L}$ (reference range, 13-33 $\mu\text{mol/L}$). The level subsequently determined the same day was 285 $\mu\text{mol/L}$. Intravenous sodium phenylacetate therapy was initiated (250-mg/kg bolus, followed by a continuous infusion at the rate of 250 mg/kg per 24 hours), along with sodium benzoate therapy (250-mg/kg bolus, followed by a continuous infusion at the rate of 250 mg/kg per 24 hours). Metronidazole hydrochloride (Flagyl) therapy was instituted to suppress colonic anaerobic flora. Intravenous 25% glucose and a continuous insulin infusion were used to suppress catabolism. On postoperative day 21, clinical signs of ICP developed, an intracranial monitoring bolt was placed, and the ICP was found to be elevated; as the plasma NH_4^+ level had risen to 1781 $\mu\text{mol/L}$, hemodialysis therapy was initiated. Just before hemodialysis was begun, the plasma NH_4^+ level was 195 $\mu\text{mol/L}$. Plasma amino acid analysis by column chromatography revealed a decreased level of glutamine at 245 $\mu\text{mol/L}$ (reference range, 285-832 $\mu\text{mol/L}$). However, the CSF glutamine level was elevated at 3910 $\mu\text{mol/L}$ (reference range, 339-865 $\mu\text{mol/L}$). Urinary orotate was undetectable. The results of analysis of urinary organic acids by gas chromatography were unremarkable. There was no evidence of liver disease.

After 24 hours of hemodialysis, the plasma NH_4^+ level was still elevated at 283 $\mu\text{mol/L}$. The sodium benzoate and sodium phenylacetate combination was switched from an intravenous to an enteral route of administration (both at 250 mg/kg per 24 hours). Also, the dosage of intrave-

nous sodium benzoate was reduced to a rate of 125 mg/kg per 24 hours. Intravenous arginine hydrochloride therapy was also instituted at the rate of 210 mg/kg per 24 hours. After 48 and 72 hours of dialysis, the plasma NH_4^+ levels were 66 and 56 $\mu\text{mol/L}$, respectively. Dialysis was discontinued after 3.5 days. Elevations of ICP up to 33 cm H_2O were treated with intravenous mannitol. There was no further evidence of increased ICP by day 7 of therapy. The patient began to regain consciousness after 10 days of therapy but later developed focal motor seizures; a computed tomogram of the head revealed asymmetrical hypodensities involving the left internal capsule and an area of hypodensity in the right superior parietal lobe, with loss of gray-white differentiation. Because enteral feeds with protein were started 5 days after the initiation of NH_4^+ -lowering therapy, we elected to continue the alternate waste nitrogen agents until 12 days after treatment. A third computed tomographic scan of the patient's head on postoperative day 30 revealed no evidence of brain edema. She required ventilatory support until postoperative day 65. There was no recurrence of the hyperammonemia.

After 2.5 months of convalescence as an inpatient, the patient was ambulatory and oriented, with normal speech, appetite, and cardiopulmonary function. A neurological examination 15 months after the operation revealed an independent woman who had returned to work as an accountant, but complained of substantial loss of short-term memory; she had occasional complex partial seizures of occipital lobe onset, which were well controlled with carbamazepine.

COMMENT

Life-threatening hyperammonemia with coma and increased intracranial pressure developed shortly after bilateral lung and heart transplantation in a woman with Ellis-van Creveld syndrome, a form of autosomal recessive short-limbed bone dysplasia, associated with postaxial polydactyly, atrial septal defect, and oral anomalies.¹⁰ The gene has been localized to 4p16. While she had the obvious stigmata of Ellis-van Creveld syndrome with complex congenital heart disease, she had demonstrated no signs or symptoms prior to her transplantation, such as intermittent obtundation, acute alterations in sensorium, or protein intolerance, which would suggest an accompanying inborn error of ammonia metabolism. She developed hyperammonemic coma after undergoing a solid-organ transplantation in association with the therapy used during the postoperative period. We now recognize this phenomenon as a complication of solid-organ transplantation, as well as a rare occurrence after bone marrow transplantation or during cancer chemotherapy.¹⁻⁸ The combination of stress, catabolism, and the use of multidrugs, such as immunosuppressants, antimetabolites, and steroids, usually along with the delivery of total parenteral nutrition, is common in all such cases.² We previously suggested that acquired hepatic GS deficiency may play a role in the pathogenesis of this syndrome, which resembles the epidemiological entity that in the past has been associated with salicylate use, Reye syndrome.² The levels of

plasma and CSF glutamine support this hypothesis in our patient. Because of her condition, however, we were unable to measure the activity of GS in liver tissue and to confirm the association of reduced hepatic activity with apparently normal brain GS activity.

The patient described herein is remarkable in that, to our knowledge, she represents the first reported case of survival in an individual with hyperammonemic coma and brain swelling after solid-organ transplantation. Although it is impossible to identify which of the modalities was crucial for successful treatment, we suggest that her survival may be attributable in part to the aggressive use of dialysis as well as the agents that are commonly used to treat hyperammonemia in congenital urea cycle defects,⁹ including sodium phenylacetate, sodium benzoate, and arginine hydrochloride. Yet, dialysis with or without these drugs has not been efficacious in the other adults with this complication whom we have treated.² Sodium phenylacetate and/or sodium benzoate have been used in patients with secondary hyperammonemia.^{3-5,11-13} Their use has been reported in association with bone marrow transplantation,^{3,4} cancer chemotherapy,⁵ and hepatic encephalopathy.¹¹⁻¹³ The most crucial aspects of this therapy may be the rapidity with which these drugs and hemodialysis are administered to any patient who is in a hyperammonemic coma with brain edema and, perhaps more importantly, the duration and degree of elevation of brain glutamine levels. The use of multiple treatment modalities, such as discontinuation of exogenous nitrogen, large amounts of calories to suppress ongoing catabolism, hemodialysis to remove ammonia and glutamine in the central nervous system, and alternate waste nitrogen agents, sodium phenylacetate and sodium benzoate, must be performed in a timely, carefully monitored fashion so that the life-threatening levels of brain glutamine derived from brain ammonia can be lowered as quickly as possible.

Our patient not only survived but was also very fortunate in that the cerebral edema did not result in major deficits in cognitive or neuromuscular functions, the major complication being a seizure disorder that has since been controlled with medication. Her only obvious neurological deficit is that of a difficulty with short-term memory. However, she was able to return to her previous work. The success of therapy in our patient may be directly related to the fact that her CSF glutamine level was only 3910 $\mu\text{mol/L}$ and not 31 070 $\mu\text{mol/L}$ as in the case reported by Tuchman et al,² in which hyperammonemia was refractory to dialysis. Of interest, 1 of the 3 survivors of an initial episode of hyperammonemic coma in a review of 9 cases associated with chemotherapy had a CSF glutamine level that was "only" 2132 $\mu\text{mol/L}$.⁶ Taken together, the data suggest that caution must be exerted in interpreting the metabolic status of the brain using either plasma NH_4^+ or glutamine levels. Extrapolation of plasma glutamine to CSF or brain levels may only serve to underestimate the critical waste nitrogen burden in brain and thus the magnitude of work of the NH_4^+ -lowering therapy. We suggest that the overall treatment schedules, including the use of drugs such as sodium benzoate, sodium phenylacetate, and arginine, as well as hemodialysis, be studied in patients with secondary hyper-

ammonemia, including those who underwent a solid-organ transplantation, a procedure that has markedly increased in frequency over the past decade.

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