Pediatric Pulmonology 30:203–206 (2000)

Cystic Fibrosis Patients With and Without Central Nervous System Complications Following Lung Transplantation

Amy B. Goldstein, MD,[1] Lawrence S. Goldstein, MD,[2] Mary K. Perl, RN, MS, NP,[3] Marcus T. Haug, PhD,[3,4] Alejandro C. Arroliga, MD,[5] and Paul C. Stillwell, MD[6]*

Summary. Central nervous system (CNS) complications occur more frequently in cystic fibrosis (CF) patients than other lung transplant recipients. The purpose of this study was to compare CF patients with and without CNS complications following lung transplantation, to identify risk factors for CNS events. Records of 21 patients with CF who underwent lung transplant between 1991–1996 were reviewed. Data were collected on multiple variables, including: age at transplant; gender; cytomegalovirus (CMV) status; cholesterol and triglyceride levels; sinusitis; percent ideal body weight (IBW); body mass index (BMI); augmented immunosuppression, acute lung rejection episodes (ALR); cyclosporine doses; electrolytes; magnesium, blood urea nitrogen (BUN), and creatinine levels; and 6-month survival. CNS complications identified were seizures, severe headaches (HA), strokes, or confusional episodes.

Eleven of 21 patients (52%) with CF had CNS events: eight had seizures, five HA, three strokes, and one confusional episode. There was no difference in age at transplant, pretransplant percent IBW or BMI, cholesterol and triglyceride levels, or number of ALR. CMV mismatch and clinical sinusitis had no effect. Cyclosporine doses did not differ between groups at 30 days, or 3 or 6 months posttransplant. Both BUN and creatinine concentrations showed a rise over time that did not differ between groups. Potassium levels were within normal limits for both groups. While sodium levels did not differ between groups pretransplant, or at 30 days or 6 months posttransplant, a decrease in sodium values was seen at the time of CNS events. There was no difference in 6-month survival.

We could not identify any pre- or posttransplant risk factors that predicted CNS events. It is likely that cyclosporine toxicity is the major cause of CNS complications. Despite the high rate of CNS events, the overall prognosis was good, and 6-month survival was not affected. **Pediatr Pulmonol. 2000; 30:203–206.**

Key words: cystic fibrosis; lung transplantation; seizures; stroke; hyponatremia; CNS complications.

INTRODUCTION

Central nervous system (CNS) complications are common following organ transplantation of all types.[1–8] Cyclosporine has been frequently implicated as the cause of neurotoxicity following both solid organ and bone marrow transplant, although the mechanism remains unclear.[1,2,5,6,9–11] CNS events have not necessarily correlated with elevated cyclosporine blood levels. An association between hypomagnesemia and cyclosporine toxicity has been reported in bone marrow transplant patients.[12] A syndrome of encephalopathy, seizures, and associated white matter changes has also been reported in liver and heart-lung transplant patients with low cholesterol levels who were receiving cyclosporine therapy, suggesting that low cholesterol increases the risk of CNS complications.[8,13] CNS complications have been associated with high-dose methylprednisolone therapy in both bone marrow and lung transplant patients.[14,15]

As lung transplantation has become a more common treatment option for end-stage lung disease, more has

[1]Section of Pediatric Pulmonary Medicine, Ohio State University College of Medicine, Columbus, Ohio.

[2]Division of Medicine, Northeastern Ohio Universities College of Medicine, Rootstown, Ohio.

[3]Transplant Center, Cleveland Clinic Foundation, Cleveland, Ohio.

[4]Department of Pharmacy, Cleveland Clinic Foundation, Cleveland, Ohio.

[5]Department of Pulmonary and Critical Care Medicine, Cleveland Clinic Foundation, Cleveland, Ohio.

[6]Section of Pediatric Pulmonology, Children's Hospital of San Diego, San Diego, California.

Presented in part at the Annual Meeting of the American College of Chest Physicians, New Orleans, Louisiana, October 1997.

*Correspondence to: Paul C. Stillwell, M.D., Section of Pediatric Pulmonology, Children's Hospital of San Diego, 3020 Children's Way MC 5070, San Diego, CA 92123. E-mail: pstillwell@chsd.org

Received 30 September 1998; Accepted 2 May. 2000.

been learned about CNS complications specific to this patient population. Goldstein et al.[2] reported that CNS complications were frequent in lung transplant recipients, and that cystic fibrosis (CF) patients had more CNS complications, particularly seizures, than did the other lung transplant groups (e.g., emphysema, pulmonary fibrosis, and idiopathic pulmonary hypertension). Similarly, Vaughn et al.,[3] at the University of North Carolina, found that the majority of their seizure complications occurred in patients with CF. The St. Louis experience with pediatric lung transplantation also found significantly more seizures in the CF patients as compared to other transplant recipients.[4] The reason for this increased predilection in CF patients is unclear. There may be metabolic, nutritional, or CF complication differences between those patients with and without CNS complications following lung transplantation. The purpose of this study was to identify risk factors for CNS complications in patients with CF by comparing CF patients with and without CNS events following lung transplantation.

MATERIALS AND METHODS

Out of 110 total lung transplants performed at the Cleveland Clinic between August 1991 and April 1996, we reviewed the records of the 21 patients with cystic fibrosis who underwent transplantation. The mean duration of follow-up posttransplant was 22 months (2 weeks to 57 months). All CF patients underwent double lung transplant and were maintained on triple immunosuppression with cyclosporine, azathioprine, and prednisone. Cyclosporine was given intravenously (IV) for the first 3 months; IV and oral doses were adjusted to maintain target levels between 250–350 ng/mL as determined by high-pressure liquid chromatography (HPLC). The patients were followed routinely with adjustments in immunosuppression based on drug levels (cyclosporine), white blood cell counts (azathioprine), blood chemistries, and complications. All patients received empirical perioperative antibiotic therapy based on preoperative sputum cultures and sensitivity results. Cytomegalovirus (CMV) prophylaxis for CMV serology mismatch (donor positive, recipient negative) consisted of gancyclovir and CMV hyperimmune globulin (Cytogam).

Abbreviations

ALR	Acute lung rejection episode
BMI	Body mass index
BUN	Blood urea nitrogen
CF	Cystic fibrosis
CMV	Cytomegalovirus
CNS	Central nervous system
CT	Computed tomography
HA	Headaches
HPLC	High-pressure liquid chromatography
IBW	Ideal body weight
IV	Intravenous
MRI	Magnetic resonance imaging
PO	Oral

Data were collected on multiple variables, including the following: age at transplant; gender; CMV status; pancreatic enzymes; cholesterol and triglyceride levels; sinusitis requiring antibiotic therapy; percent ideal body weight (IBW); body mass index (BMI); augmented immunosuppression; acute lung rejection episodes (ALR) requiring steroid pulses; cyclosporine doses; electrolytes; magnesium, blood urea nitrogen (BUN), and creatinine levels; and 6-month survival.

Definitions

Seizures were events either witnessed by a healthcare provider or diagnosed by description of tonic clonic activity with loss of consciousness; *severe headaches* were those headaches (HA) not responsive to over-the-counter analgesics; *strokes* were identified as part of a neurologic evaluation by consulting neurologists, including imaging studies by either computed tomography (CT) or magnetic resonance imaging (MRI); and *confusional episodes* were defined as a decrease in cognitive functioning. *Sinusitis episodes* were those requiring antibiotic therapy for acute sinusitis or exacerbations of chronic sinusitis; radiographic confirmation was not required. *CMV mismatch* was defined as donor-positive and recipient-negative CMV serology. *Acute lung rejection episodes* were those rejection episodes treated with high-dose methylprednisolone pulses after confirmation by transbronchial biopsy.

Patients who had a seizure, complained of severe headache, or had evidence of a stroke or a confusional episode were included in the CNS complication group.

Statistical Analysis

Group means were compared by *t*-test and proportions by X^2, with significance defined as $P < 0.05$ (two-tailed) (StatMost for Windows, version 2.5; DataMost Corp., Salt Lake City, UT).

RESULTS

Eleven of the 21 patients (52%) with cystic fibrosis had a total of 17 CNS complications. These included eight patients with seizures, five with HA, three with strokes, and one with a confusional episode. The CNS events occurred between days 4–132 posttransplant (mean day 44).

Patient characteristics, including demographic, nutritional, acute rejection, CMV serologic status, sinusitis, and survival data are presented in Table 1, with age being

TABLE 1—Patient Characteristics: Comparison of CF Patients With and Without CNS Complications[1]

Variable	Without CNS complications (N = 10)	With CNS complications (N = 11)	*P*-value
Age (years)	26.0 ± 8.3	27.2 ± 7.7	0.73
% IBW	85.8 ± 10.0	79.9 ± 13.8	0.31
BMI	20.0 ± 2.5	18.1 ± 3.2	0.18
Cholesterol (mg/dL)	207 ± 89.7	184 ± 43.7	0.57
Triglycerides (mg/dL)	182 ± 87.4	232 ± 129.0	0.51
No. of ALRs	1.1 ± 0.7	1.6 ± 1.86	0.40
CMV mismatch	3/10	2/11	0.65
Sinusitis	30%	55%	0.25
6-month survival	70%	82%	0.26

[1]Mean ± standard deviation. IBW, ideal body weight; BMI, body mass index; ALR, acute lung rejection treated with high-dose methylprednisolone; sinusitis, episodes treated with antibiotics.

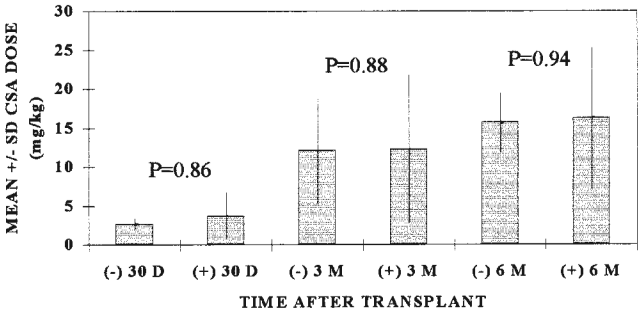

Fig. 1. Cyclosporine dose: 30 days, 3 months, and 6 months posttransplant. The dose is in mg/kg, with mean (± SD) shown. D, days; M, months; −, group without CNS complications; +, group with CNS complications; CSA, cyclosporin dose. The 30-day dose is intravenous, and the 3- and 6-month doses are oral. *P*-values are shown.

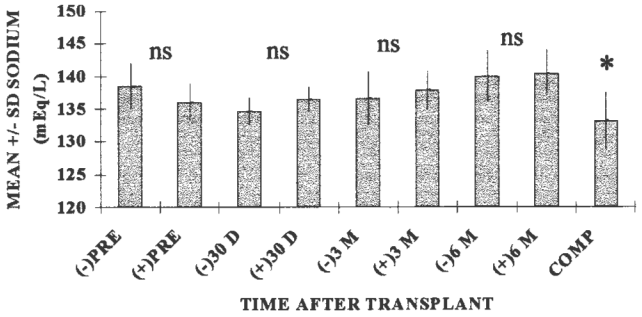

Fig. 2. Serum sodium levels pretransplant, 30 days, 3 months, and 6 months posttransplant, and at the time of complications. Values are in mEq/L, with mean (± SD) shown. D, days; M, months; Comp, time of complication; −, group without CNS complications; +, group with CNS complications; ns, no significant difference between + and − groups (*P* > 0.05). *Significant difference from pretransplant value (*P* < 0.05).

age at transplant, and percent IBW and BMI being immediate pretransplant values. Mean percent IBW at the time of CNS complication was 83.1, and did not differ from pretransplant values ($P = 0.21$).

Figure 1 shows that cyclosporine doses, in milligrams per kilogram, were not different between groups. Thirty-day doses were IV, while 3- and 6-month doses were oral. Sodium and creatinine values are presented in Figures 2 and 3, respectively. At the time of CNS complications, 4 of 11 sodium values fell below 130 mEq/L (128–129 mEq/L). Data on potassium levels showed that they were normal for both groups pretransplant, at 30 days, and at 6 months posttransplant; values at the time of CNS events were also in the normal range. There was no significant difference in potassium concentrations between groups at any time, and no difference between pretransplant status or 6 months posttransplant and the time when a CNS event was noted ($P = 0.27$ and 0.46, respectively). Blood urea nitrogen and creatinine levels rose from pretransplant to 6 months posttransplant. Those without CNS complications had a pretransplant mean BUN of 11.8 mg/dL, and creatinine of 0.72 mg/dL, which increased to 27.7 mg/dL and 1.4 mg/dL, respectively, at 6 months posttransplant. The mean pretransplant BUN and creatinine for those who had CNS complications was 13 mg/dL and 0.8 mg/dL, respectively, increasing to 30.6 mg/dL and 1.6 mg/dL, respectively, at 6 months posttransplant. There was no significant difference between groups at any point. Magnesium levels showed no significant difference between groups pretransplant (mean for those without CNS complications, 1.5 mg/dL; with CNS complications, 1.3 mg/dL). There was no significant change in these levels at the time of CNS complications (mean at CNS complication, 1.7 mg/dL; $P = 0.07$).

Prognosis for survivors was favorable, with only the stroke patients showing long-term sequelae. Two of three stroke patients survived; both had evidence of residual weakness. One stroke patient required chronic anticonvulsant therapy for secondary seizures. Six-month survival did not differ between groups, with 70% 6-month survival for those without CNS complications, and 82% 6-month survival for those with CNS events (Table 1).

DISCUSSION

CNS complications occur more frequently in CF patients than other lung transplant recipients.[2,3] The most common were seizures and HA, with strokes and confusional episodes occurring less frequently. Retrospective reviews of the neuroimaging studies of transplant recipients have suggested that the majority of these findings were related to cyclosporine toxicity.[2,16,17] We could not identify any pre- or posttransplant risk factors that predicted CNS events. Nutritional status, which may reflect the severity of malabsorption in CF patients, did not differ between groups. Cholesterol levels also did not differ between groups, and neither group demonstrated hypo-

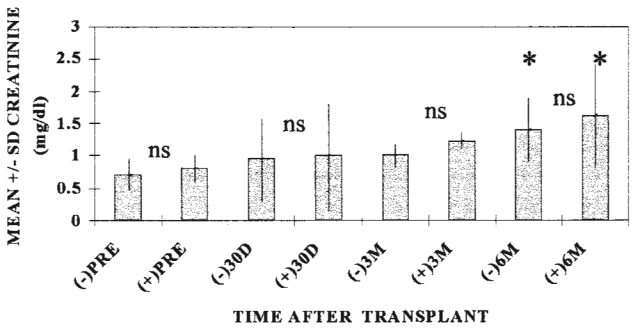

Fig. 3. Serum creatinine levels pretransplant, and 30 days, 3 months, and 6 months posttransplant. Levels are in mg/dL with mean (± SD) shown. D, days; M, months; −, group without CNS complications; +, group with CNS complications; ns, no significant difference between + and − groups ($P > 0.05$). *Significant increase compared to pretransplant values ($P < 0.05$).

cholesterolemia, which has been associated with CNS events in other transplant patients on cyclosporine.[8,13] Similarly, pulses of high-dose methylprednisolone given as therapy for acute rejection did not appear to be a risk factor in our population.

Electrolyte abnormalities are often associated with CNS events, particularly seizures. Hypomagnesemia, which has been associated with cyclosporine immunosuppression as well as seizures, was not seen, either pretransplant or at the time of CNS events. Routine monitoring of magnesium levels and magnesium replacement therapy has probably helped to prevent this occurrence. Although sodium levels did not differ between groups, a minor decrease in sodium was seen at the time of CNS events, with four patients having levels of 128 or 129 meq/L. While these values alone would be unlikely to cause seizures, they may contribute to lowering the seizure threshold in patients also receiving cyclosporine.

Renal dysfunction may affect both blood pressure and drug clearance, and therefore may also contribute to CNS complications. Only one patient had an acute hypertensive episode associated with her stroke. Both groups showed a similar rise in BUN and creatinine levels over time, but there were no differences between groups. This was probably due to the cyclosporine therapy. Antibiotic use, particularly imipenem, was not more common in the CNS complication group.

We do not know why CF transplant patients have a greater incidence of CNS events than other lung transplant patients.[2] The neuroimaging findings were similar regardless of the underlying lung disease.[2] Our data do not support a difference in cyclosporine metabolism, and we are unaware of a mechanism by which cyclosporine should alter cystic fibrosis transmembrane regulator protein function.

Despite the high frequency of CNS complications in our CF patients, overall prognosis was good, with only two patients showing long-term sequelae. Six-month survival was not affected. We recommend vigilance in monitoring cyclosporine, magnesium, and sodium levels, as well as potential drug-drug interactions. In addition, prompt attention should be paid to any neurologic complaints.

REFERENCES

1. Patchell RA. Neurological complications of organ transplantation. Ann Neurol 1994;36:688–703.
2. Goldstein LS, Haug M, Perl J II, Perl MK, Maurer JR, Arroliga AC, Mehta AC, Kirby T, Higgins B, Stillwell PC. Central nervous system complications after lung transplantation. J Heart Lung Transplant 1998;17:185–191.
3. Vaughn BV, Ali II, Olivier KN, Lackner RP, Robertson KR, Messenheimer JA, Paradowski LJ, Egan TM. Seizures in lung transplant recipients. Epilepsia 1996;37:1175–1179.
4. Sweet SC, Spray TL, Huddleston CB, Mendeloff E, Canter CE, Balzer DT, Bridges ND, Cohen AH, Mallory GB. Pediatric lung transplantation at St. Louis Children's Hospital, 1990–1995. Am J Respir Crit Care Med 1997;155:1027–1035.
5. Martin AB, Bricker JT, Fishman M, Frazier OH, Price JK, Radovancevic B, Louis PT, Cabalka AK, Gelb BD, Towbin JA. Neurologic complications of heart transplantation in children. J Heart Lung Transplant 1992;11:933–942.
6. Reece DE, Frei-Lahr DA, Shepherd JD, Dorovini-Zis K, Gascoyne RD, Graeb DA, Spinelli JJ, Barnett MJ, Klingemann HG, Herzig GP, Phillips GL. Neurologic complications in allogeneic bone marrow transplant patients receiving cyclosporin. Bone Marrow Transplant 1991;8:393–401.
7. Christe W. Neurological disorders in liver and kidney transplant recipients. Transplant Proc 1994;26:3175–3176.
8. De Groen PC, Aksamit AJ, Rakela J, Forbes GS, Krom RA. Central nervous system toxicity after liver transplantation: the role of cyclosporine and cholesterol. N Engl J Med 1987;317:861–866.
9. Berden JHM, Hoitsma AJ, Merx JL, Keyser A. Severe central nervous system toxicity associated with cyclosporin. Lancet 1985; 1:219–220.
10. McManus RP, O'Hair DP, Schweiger J, Beitzinger J, Siegel R. Cyclosporine associated central neurotoxicity after heart transplantation. Ann Thorac Surg 1992;53:326–327.
11. Lane RJM, Roche SW, Leung AAW, Greco A, Slange LS. Cyclosporine neurotoxicity in cardiac transplant recipients. J Neurol Neurosurg Psychiatry 1988;51:1434–1437.
12. Thompson CB, Sullivan KM, June CH, Thomas ED. Association between cyclosporine neurotoxicity and hypomagnesaemia. Lancet 1984;2:1116–1120.
13. Cooper DKC, Novitzky D, Davis L, Huff JE, Parker D, Schlesinger R, Sholer C, Zuhdi N. Does central nervous system toxicity occur in transplant patients with hypocholesterolemia receiving cyclosporine? J Heart Transplant 1989;8:221–224.
14. Durrant S, Chipping PM, Palmer S, Gordon-Smith EC. Cyclosporin A, methylprednisolone, and convulsions. Lancet 1982;2: 829–830.
15. Boogaerts MA, Zachee P, Verwilghen RL. Cyclosporin, methylprednisolone, and convulsions. Lancet 1982;2:1216–1217.
16. Scheinman SJ, Reinitz ER, Petro G, Schwartz RA, Szmalc FS. Cyclosporine central neurotoxicity following renal transplantation: report of a case using magnetic resonance images. Transplantation 1990;49:215.
17. Hughes RL. Cyclosporine related central nervous system toxicity in cardiac transplantation. N Engl J Med 1990;323:420–421.