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Neurologic complications following lung transplantation

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ABSTRACT

Background: Neurologic complications are frequent after solid organ transplantation, but their spectrum in lung transplant recipients has not been characterized.
Methods: Retrospective analysis of medical records of 132 consecutive adult lung allograft recipients transplanted at the University of Pittsburgh Medical Center between 2001 and 2003 with a follow-up until December 31, 2005.
Result: Neurologic complications were reported in 68% of lung transplant recipients. Most common complications were impairment of consciousness (25%), neuromuscular complications (21%) and headaches (20%). The presence of neurologic complications did not affect posttransplant survival. Neurologic complications were commonly related to immunosuppressant neurotoxicity (17%) and opportunistic infections (11%). There was a trend for an increased frequency of seizures and headaches in recipients with cystic fibrosis ($p>0.05$).
Conclusions: Neurologic complications are a significant source of morbidity in lung transplant recipients. High prevalence of immunosuppressant toxicity is attributable to higher immunosuppression needs for effective prevention of allograft rejection. Frequent opportunistic infections are associated with complications related to systemic and CNS infections and toxicity of antibiotics. Patients with cystic fibrosis may be at higher risk of neurologic complications, but larger studies are needed to corroborate this finding and fully characterize the spectrum of neurologic complications following lung transplantation.

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1. Introduction

Advances of surgical techniques and more effective immunosuppression protocols over the last quarter of century enabled lung transplantation to evolve into an effective therapy for end-stage respiratory failure [1]. In the current era, transplant recipients live longer with improved quality of life compared to earlier periods. However, due to a higher incidence of rejection than with most other solid organ allografts, lung transplant recipients generally require greater immunosuppression leading to a higher rate of complications [1]. Clinical course after transplantation is still impeded by various surgical and medical complications, and neurologic complications have been reported in 30–60% of solid organ allograft recipients [2]. The etiology of posttransplant complications is usually related to the primary disease causing organ failure, surgical complications of the transplant procedure, the need for immunosuppression and complex toxic or metabolic disturbances. Chronic immunosuppression is associated with persistent risk of opportunistic infections and immunosuppressant neurotoxicity. In recent years, overall improvement in patient survival shifted the spectrum of post-transplant complications from acute and perioperative events towards subacute and chronic complications. There are only a few reports describing neurologic complications after lung transplantation in adult and pediatric recipients with an increased frequency of neurologic complications reported in recipients with cystic fibrosis [3–7].

In this report we describe the spectrum of neurologic complications after lung transplantation in adult allograft recipients in a large lung transplant program.

2. Methods

We performed a retrospective analysis of medical records of all consecutive adult recipients of lung allografts transplanted at our medical center between 2001 and 2003. We have recorded pattern, time of onset, type and etiology of neurologic complications during follow-up until December 31, 2005. Analysis included review of clinical notes, laboratory results, imaging studies and autopsies. Statistical analysis included Kaplan Meier survival curve, Wilcoxon, log rank test, Fisher exact and χ^2 tests. Study end-points were end of

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Table 1
Demographic characteristics of lung transplant recipients.

Age, average ± SD (range), years	49.57 ± 12.53 (18–70)
Gender	M 69; F 63
Re-transplant	4
Allograft	
Unilateral	66
Bilateral	63
Heart–lung	3
Causes of lung failure	
COPD/emphysema	55
Cystic fibrosis	23
IPF	22
Connective tissue diseases[a]	10
Pulmonary hypertension	7
Sarcoidosis	7
Other causes[b]	8

[a] Systemic sclerosis — 4, CREST — 2, Sjogren's, mixed connective tissue disorder, dermatomyositis, rheumatoid arthritis — 1 each.
[b] Silicosis — 5, eosinophilic granuloma — 1, Castleman's disease — 1, graft-versus-host disease — 1; COPD — chronic obstructive pulmonary disease; IPF — idiopathic pulmonary fibrosis.

follow-up on December 31, 2005, or death of a patient. The study was approved by our institutional IRB.

3. Results

There were 132 consecutive adult recipients of lung allografts. Recipients were 52% male with a mean age of 49.6 years (Table 1). Neurologic complications were observed in 90 lung transplant recipients (68%), with a similar overall frequency of neurologic complications across different causes of primary lung failure (Table 2). There was a trend for an increased prevalence of seizures (17% vs. 5.5%) and headaches (30.4% vs. 19.7%) in patients with cystic fibrosis (CF) but this was not statistically significant (χ^2; $p>0.05$). There were no fatal outcomes directly related to neurologic complications. The presence of neurologic complications did not significantly affect survival after lung transplantation (Kaplan Meier — not shown; Wilcoxon, $p=0.929$; log rank $p=0.938$). Due to retrospective nature of our study we could not separate with certainty recurrent headaches from new onset of headaches after transplantation, but there was no reported history of prior seizures or strokes in any of allograft recipients.

Most common posttransplant complications were alterations of consciousness ($n=33$; 25%), neuromuscular complications ($n=28$; 21%), and headaches ($n=26$; 20%)(Table 2). Additionally, there were 7 transplant recipients with ischemic strokes (5%), 2 with intracranial hemorrhages (1.5%), 10 with seizures (8%), and 1 with opportunistic CNS infection (0.7%).

3.1. Alterations of consciousness

Impaired consciousness was reported in 33 recipients (25%; 57 events). Most common causes included calcineurin-inhibitor neurotoxicity (11 events), metabolic disturbances ($n=12$), systemic and CNS infections ($n=8$), and brain hypoxia or anoxia ($n=7$). A single cause could not be established with certainty in 1/3 of events ($n=19$). Impairment of consciousness was most common in first 30 days ($n=22$) and from days 31–180 after transplantation ($n=14$). Alterations of consciousness related to tacrolimus- and cyclosporine neurotoxicity and anoxic brain injury were more common during first 30 days after transplantation (5 events each).

3.2. Seizures

Seizures were reported in 10 allograft recipients (8%; 15 events), and causes included tacrolimus neurotoxicity (3 events), toxicity of other medications ($n=2$; imipenem and cefepime), anoxic brain injury ($n=3$), stroke ($n=2$) and etiology remained uncertain for remaining 5 events.

3.3. Cerebrovascular complications

Cerebrovascular complications were observed in 9 patients (7%). Ischemic strokes mostly presented early (5 of 7 events within first 30 days, 2 after >1 year), including three perioperative cardioembolic ischemic strokes within 7 days of transplantation procedure. Overall, etiology of ischemic strokes was predominantly cardioembolic (6 recipients, including one with atrial fibrillation) and was thrombotic in only one patient. Subarachnoid hemorrhage was reported in 2 patients with gram-negative sepsis (1.5%). Cerebrovascular complications were less common in patients with CF and idiopathic pulmonary fibrosis, but this was not statistically significant (4% vs. 8%).

3.4. Headaches

Headaches were reported in 26 recipients (20%; 35 events). Etiology of headaches was mostly related to exacerbation of pre-existing migraines (9 events), calcineurin inhibitor neurotoxicity ($n=7$) and chronic sinusitis ($n=7$). Other causes included adverse effects of mycophenolate, esomeprazole and a case of cryptococcal meningitis (1 each), while etiology was not determined in the remaining 9 cases.

3.5. Neuromuscular complications

Twenty-eight recipients (21%) developed neuromuscular complications including polyneuropathies (8%), mononeuropathies (7%), myopathies (5%) and plexopathies (1.5%). Polyneuropathy was reported in 11 recipients and causes included diabetic (6 cases) and toxic neuropathies ($n=2$; ethambutol and linezolid toxicity), while etiology remained uncertain in 3 cases. Mononeuropathies included phrenic ($n=3$), recurrent laryngeal and deep peroneal (2 each), and facial and ulnar neuropathies (1 each). There were also 2 cases of brachial plexopathies and 6 cases of myopathies (critical illness myopathy — 4; uncertain cause — 2 cases).

Table 2
Neurologic complications and causes of lung failure.

Primary lung disorder	*n*	Mean age (years)	Neurologic complications (%)	Seizures	CNS infection	Headache	Neuromuscular complications	Impairment of consciousness	Stroke[a]
COPD	55	55.9	39 (71)	3	1	15	7	17	5
CF	23	30.7	16 (70)	4	0	7	6	3	1
IPF	22	54.4	14 (64)	0	0	2	4	6	1
CTD	10	46.1	5 (50)	1	0	0	1	1	1
Sarcoid	7	49.7	4 (57)	1	0	1	3	2	1
PulHTN	7	48.9	5 (71)	0	0	1	4	1	0
Other	8	50.1	7 (88)	2	0	2	3	1	0
Total (%)	132		90 (68)	10 (8)	1 (1)	26 (20)	28 (21)	33 (25)	9 (7)

[a] Including ischemic strokes and intracerebral hemorrhage; COPD — chronic obstructive pulmonary disease; CF — cystic fibrosis; IPF — idiopathic pulmonary fibrosis; CTD — connective tissue diseases; PulHTN — pulmonary hypertension.