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ORIGINAL ARTICLE

Posterior reversible encephalopathy syndrome after lung transplantation: Risk factors and management

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Abstract

Introduction: Posterior reversible encephalopathy syndrome is a rare neurologic complication that can occur under immunosuppressive therapy with CNI after organ transplantation.

Methods: We retrospectively reviewed medical records of 545 patients who underwent lung transplantation between 2012 and 2019. Within this group, we identified 30 patients with neurological symptoms typical of PRES and compared the characteristics of patients who were diagnosed with PRES ($n = 11$) to those who were not ($n = 19$).

Results: The incidence of PRES after lung transplantation was 2%. Notably, 73% of the patients with PRES were female and the mean age was 39.2. Seizure (82% vs. 21%, $p = .002$) was the most common neurological presentation. The risk of developing PRES was significantly associated with age (OR = .92, $p < .0001$) and having cystic fibrosis (CF) (OP = 10.1, $p < .0001$). Creatinine level (1.9 vs. 1.1 mg/dl, $p = .047$) and tacrolimus trough level (19.4 vs. 16.5 ng/ml, $p = .048$) within 1 week prior to neurological symptoms were significantly higher in patients with PRES.

Conclusion: Renal insufficiency and high tacrolimus levels are associated with PRES. A change of immunosuppressive drug should be done after confirmed PRES diagnosis or immediately in case of severe neurological dysfunction to improve neurological outcomes and minimize the risk of early allograft rejection.

KEYWORDS
encephalopathy, immunosuppressant, lung transplantation, neurologic complication, neurotoxicity, tacrolimus

1 INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES), first described by Hinchey,[1] is a rare syndrome characterized by neurological symptoms including headache, seizure, altered level of consciousness, visual abnormalities, or other neurological deficiencies like paresthesia.[2] It is associated with hypertension, autoimmune diseases, eclampsia, renal failure,[3] vascular diseases, infection, sepsis, shock,[4] and most recently with Covid-19 pneumonia.[5–7] It can also occur under immunosuppressive therapy with calcineurin inhibitors (CNI) or after chemotherapy.[1,4] PRES is usually diagnosed with MRI of the brain, which shows vasogenic edema of the white matter typically located bilaterally in the

subcortical and cortical areas of the occipital and parietal lobes, which are supplied by the posterior circulation.[8,9] However, other areas such as basal ganglia, brain stem, thalami, and frontal lobes can also be involved and are summarized as atypical PRES.[10,11] Depending on the location and the extent of lesions, neurological symptoms vary.

There are several theories about the mechanism of brain edema in PRES. It can occur as a consequence of vasospasm of blood vessels, which causes hypoperfusion and endothelial dysfunction with increased vascular permeability.[12–14] The vasoconstrictive effect of CNIs, specifically of cyclosporine A (CsA) through increased production of endothelin was already shown[15,16] and can be detected with a duplex sonography, a computed tomography angiography or a magnet resonance angiography of these vessels.[17,18] Another theory suggests that the disruption of vascular autoregulation as a result of severe hypertension causes cerebral vasodilatation leading to a blood-brain barrier (BBB) dysfunction[19] and extravasation of fluid into the brain parenchyma.[20,21] Magnesium, as a competitive antagonist of calcium, has a vasodilatory effect and can prohibit the development of vasogenic edema.[22] Therefore, hypomagnesemia, which appears under therapy with CNI[23–26] could promote the vasoconstriction of cerebral vessels. All these theories presume as a common cause of PRES the dysfunction of cerebral autoregulation.

PRES after solid organ transplantation (SOT) is very rare. Most previous studies present only case reports.[27,28] A few retrospective studies have been performed to evaluate the clinical and imaging features of PRES after liver transplantation[29] and SOT including lung transplantation.[30–32] There is no specific therapy regimen other than changing the immunosuppressive drug.[33] Therefore, early diagnosis and intervention is the key to minimize the damage.[34]

The purpose of this study is to analyze the risk factors, clinical presentation, and diagnostic features of PRES after lung transplantation to understand the incidence of PRES and develop diagnostic and therapeutic strategies.

1 | MATERIALS AND METHODS

1.1 | Patients with neurologic complications

After approval of the Ethics committee (21-0125), we retrospectively reviewed medical records of 545 patients who underwent double lung transplantation between January 2012 and December 2019 at the Ludwig Maximilian University Hospital in Munich, Germany. We searched for neurological consultations documented in the electronic database of the hospital. Of 545 patients, 151 patients developed neurological symptoms after transplantation and were examined by a neurologist. The clinical and radiological data of these patients were carefully evaluated to categorize the neurologic complications.

1.2 | Patients with PRES typical symptoms

We evaluated a subgroup of all patients with suspected cases of PRES presenting neurological symptoms typical of PRES such as headache, seizure, vision change, altered level of consciousness, delirium, and other neurological deficiencies. In this group, we compared characteristics and clinical data between patients with a confirmed diagnosis of PRES and patients without PRES. We analyzed co-variables such as gender, age, underlying disease, hypertension, hypomagnesaemia, peek creatinine level, maximum Tacrolimus (TAC) level 1 week prior to neurologic event to find out the risk factors for developing PRES. In order to confirm the diagnosis, all imaging and diagnostic results of these patients, including CT scan and MRI of the brain, sonography of brain vessels, electroencephalography (EEG), and cerebrospinal fluid (CSF) samples were carefully assessed. Imaging findings were documented by radiologists and systematically reviewed by a neuroradiologist for characteristic features of immunosuppressive-induced neurotoxicity and PRES. The cases were confirmed as PRES, if they showed a complete or partial expression of typical PRES pattern in radiological imaging with a clinical sign of neurotoxicity and reversibility on follow-up imaging or reversibility of the clinical presentation.

With the suspected diagnosis of PRES, the immunosuppressive regimen was switched from TAC to CsA. The switch was done immediately in case of severe neurological symptoms or after confirmed diagnosis with MRI of the brain, which was performed approximately within 3 days after the first symptom. MTOR inhibitors, such as Everolimus or Sirolimus were used alone or in combination with CsA later on, if the patients showed progressive brain edema in MRI with persistent neurological symptoms. Additionally, anticonvulsants in case of seizures and antihypertensive drugs to adjust blood pressure were applied. Hypertension and severe hypertension were defined as systolic blood pressure over 140 and 180 mmHg. Patients showing vasospasms of brain vessels in the duplex sonography have received nimodipine to vasodilate the intracranial vessels. As a follow-up, the results of neurological and radiological examinations after therapy were assessed.

1.3 | Imaging evaluation

Unenhanced head CT imaging was performed in craniocaudal helical acquisition (slice thickness 2 and 5 mm, respectively) with reconstructions in the coronal and sagittal planes (slice thickness 2 and 3 mm, respectively). MR imaging included axial diffusion weighted imaging (DWI) with a slice thickness of 5 mm, axial TSE T2-weighted imaging (3–5 mm), axial fluid attenuation inversion-recovery (FLAIR) imaging (5 mm), axial and sagittal TSE T1-weighted imaging (5 mm) before and after intravenous administration of a macrocyclic Gadolinium-based contrast agent (gadoteric acid, Dotagraf) and arterial time-of-flight (TOF) MR-angiography with 3-dimensional reconstructions. Sonography of blood vessels supplying blood circulation to the brain was performed and documented by a neurologist.

1.4 | Transplantation management

Patients received a triple immunosuppression with Tacrolimus (TAC) combined with prednisolone and mycophenolate mofetil (MMF). Accepted therapeutic morning trough blood level of TAC in the first 6

months after lung transplantation was between 12 and 15 ng/ml. With the suspected diagnosis of PRES, immunosuppressive regimen was switched from TAC to CsA with the target morning trough blood level of 160–200 ng/ml. When CsA was administered in combination with mTOR inhibitors the target levels were 80–100 ng/ml and 4–6 ng/ml, respectively.

3–4 weeks after transplantation or at any time in case of reduced organ function, a transbronchial biopsy and a quarterly screening for donor-specific human leukocyte antigen (HLA)-antibodies were performed. Acute cellular rejection was always biopsy-proven defined according to the International Society of Heart and Lung Transplantation (ISHLT) guidelines.[35] In our study population only minimal rejections (A1) were observed, which were treated with steroid pulse therapy. Antibody-mediated rejection (AMR) has been assessed according to the Consensus guidelines,[36] if donor-specific HLA-antibodies were detected. Patients with suspected AMR received immunoglobulin and plasmapheresis with or without anti-CD20 antibody treatment.

All recipients received prophylactic antibacterial, antifungal, and antiviral treatment for at least 3 months.

1.5 | Statistical assessment

Statistical analysis was performed with the software SPSS Version 26 and R version 4-0 with R-Studio. Continuous variables were reported as means with standard deviation (SD), and categorical variables as absolute and relative frequencies. Categorical variables were compared between groups using χ^2-test or Fisher's exact test (when cell numbers were <6). We used Shapiro Wilkes test to test for normal distribution of continuous variables. Depending on test for normality continuous variables were compared with Student's *t*-test and Mann-Whitney-U test. Additionally, we used univariable logistic regression models in the whole population, as well as in the population of patients suspected of PRES, to analyze factors associated with the development of PRES. Statistical significance was considered to exist, if the *p*-value was under .05.

TABLE 1 Common neurologic complications after lung transplantation

Lung transplantation 2012–2019	*n* = 545
Neurologic diagnosis	**Incidence *n* (%)**
CIP/CIM	29 (5.3)
Seizure	21 (3.9)
Encephalopathy	20 (3.7)
Ischemia, TIA, cerebral infarction	14 (2.6)
Delirium	11 (2.0)
PRES	11 (2.0)
Headache, migraine	11 (2.0)
Paresis of extremities	10 (1.8)
Other nerve damages	10 (1.8)
Intracerebral hemorrhage	9 (1.6)
Polyneuropathy	5 (.9)
Tremor	4 (.7)

Abbreviations: CIP/CIM, critical illness polyneuropathy/myopathy; PRES, posterior reversible encephalopathy syndrome; TIA, transient ischemic attack.

TABLE 2 Demographics and primary diseases of patients diagnosed with PRES after lung transplantation compared to the whole study population

	No PRES (*n* = 534)		PRES (*n* = 11)		
	Mean	SD	Mean	SD	*p*-value
Age	51.3	12.4	39.2	14.6	***.0002***
	n	%	*n*	%	
Male	294	55.1	3	27.3	.12
Female	240	44.9	8	72.7	
CF	79	14.8	7	63.6	***.0004***
Other diseases	455	85.2	4	36.4	

Abbreviation: CF, cystic fibrosis.

2 | RESULTS

2.1 | Neurological symptoms after lung transplantation

From 545 patients, who underwent lung transplantation between 2012 and 2019 at the University Hospital of Munich, 151 (27.7%) patients developed neurological symptoms during the early phase after transplantation. The most common neurologic complication was critical illness polyneuropathy/myopathy (CIP/CIM) with an incidence of 5.3% followed by seizures (3.9%). Encephalopathy of varying etiology such as septic, metabolic, or vascular was observed in 3.7% of patients. Ischemia and cerebral infarction were diagnosed in 2.6% of patients, followed by intracerebral hemorrhage, which was confirmed in 1.6% of all cases. PRES had the same incidence of 2% as delirium and headache of other etiologies (Table 1).

2.2 | Demographics (PRES-patients vs. whole study population)

Patients diagnosed with PRES ($n = 11$) were much younger with a mean age of 39.2 compared to the whole study population ($n = 534$) with a mean age of 51.3 years ($p = .0002$). Although 55.1% of patients who received lung transplantation were male, 72.7% of the patients diagnosed with PRES were female. The prevalence of cystic fibrosis (CF) in patients with PRES was significantly higher (63.6%) compared to the prevalence of CF in patients without PRES (14.8%) ($p = .0004$, Table 2). Additionally, the univariable logistic regression analysis showed that the risk of developing PRES was significantly associated with age (OR = .92, $p < .0001$) and having CF (OP = 10.1, $p < .0001$), but not with sex (Table 4).

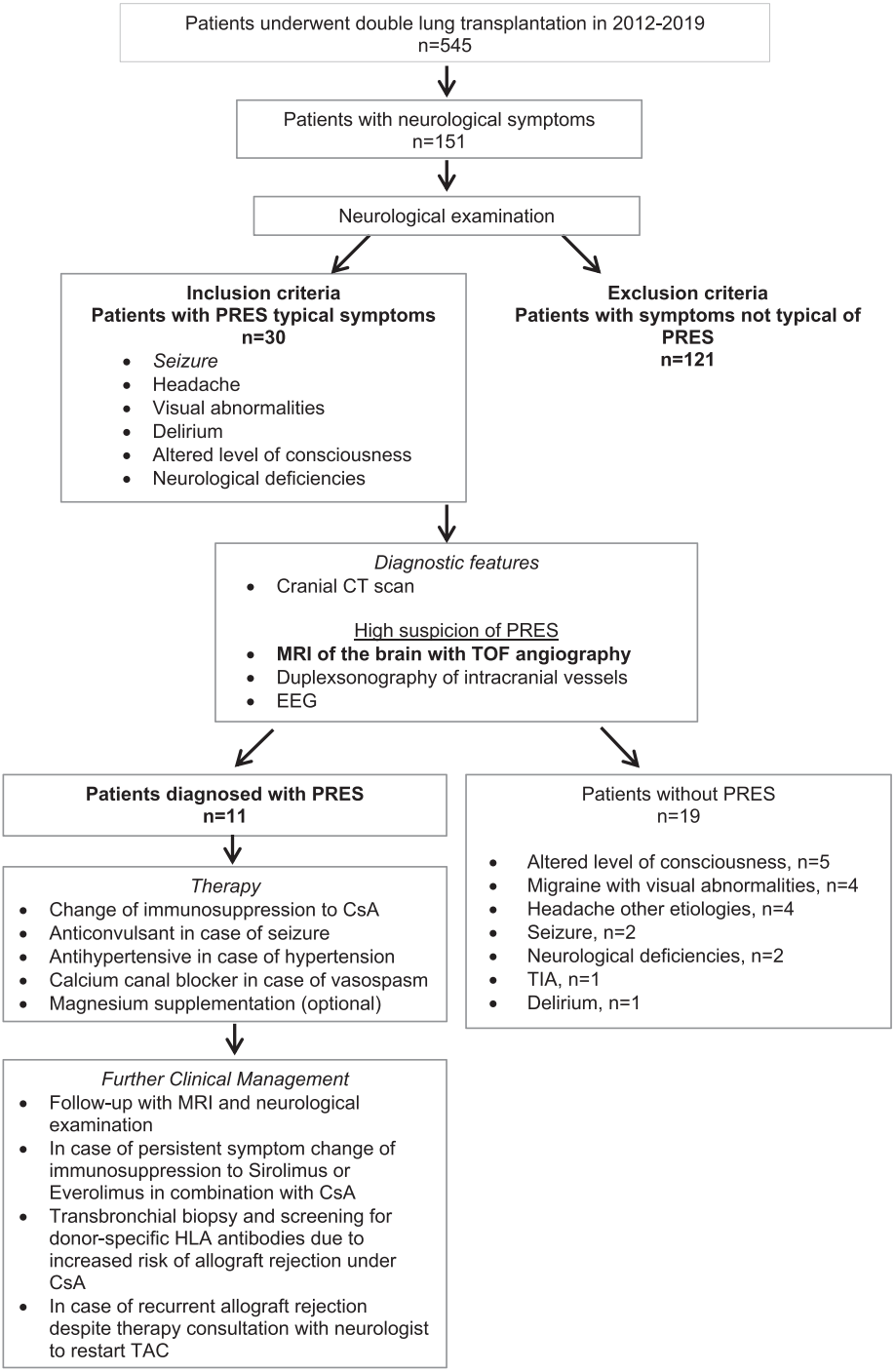

FIGURE 1 Clinical presentation, diagnosis, and treatment of PRES after lung transplantation.

2.3 | PRES after lung transplantation

Of 30 patients presenting PRES typical neurological symptoms, 11 have been diagnosed with PRES due to typical radiological features and reversibility after changing immunosuppressive regimen. In 19 patients, the suspected diagnosis of PRES could be ruled out (Figure 1). The following results are based on the comparison of these two patient groups.

2.4 | Symptoms, clinical, and laboratory parameters

The average time between transplantation and the first symptom was 50.5 days (range 7–189, Table 3) for patients with PRES. Five patients (45.5%) developed PRES within 15 days as an early onset and only one patient developed PRES after 6 months (Figure 2). Significantly higher proportion of patients diagnosed with PRES presented seizures

TABLE 3 Demographics, clinical, radiological, and laboratory characteristics of 30 patients with PRES typical neurological symptoms after lung transplantation divided into two groups: Patients diagnosed with PRES (n 11) and patients without a confirmed diagnosis of PRES ($n = 19$)

Patients suspected of PRES	$n = 30$		
Patients diagnosed with PRES	Yes	No	
	$n = 11$	$n = 19$	*p*-value
Demographics			
Gender	$m = 3, f = 8$	$m = 6, f = 13$	.571
Age	39.2 (+/− 14.6)	40.3 (+/− 13.5)	.81
Primary disease			
CF	7 (63.6%)	10 (52.6%)	.421
IPF	1 (9.1%)	2 (10.5%)	.702
COPD	2 (18.2%)	1 (5.3%)	.298
PH	0 (0%)	5 (26.3%)	.082
EAA	1 (9.1%)	1 (5.3%)	.607
Symptoms			
Day between transplant and the first symptom	50.5 (+/− 57.3)	31.9 (+/−28.9)	1.00
Seizure	*9 (81.8%)*	*4 (21.1%)*	.002
Headache	7 (63.6%)	8 (42.1%)	.225
Somnolence	5 (45.5%)	9 (47.4%)	.610
Neurological deficiency	6 (54.5%)	10 (52.6%)	.610
Visual symptoms	3 (27.3%)	6 (31.6%)	.571
Delirium	1 (9.1%)	5 (26.3%)	.261
Laboratory values			
Creatinine max. (mg/dl)	*1.9 (+/− 1.4)*	*1.1 (+/− .7)*	***.047****
Creatinine-clearances (ml/min)	48.9 (+/− 43.2)	71.5 (+/− 43.4)	.241
Tacrolimus-level max. (ng/ml)	*19.4 (+/− 4.9)*	*16.5 (+/− 2.8)*	***.048***
Interleukine-6 (ng/ml)	27.5 (+/− 22.2)	58.8 (+/− 135.0)	.832*
Leukocyte (G/l)	9.2 (+/− 6.7)	14.0 (+/− 8.4)	.102*
CRP (mg/dl)	2.4 (+/− 2.6)	4.0 (+/− 4.5)	.207
Albumin (g/dl)	2.8 (+/− .6)	2.8 (+/− .6)	.821
Magnesium (mmol/l)	.6 (+/− .2)	.8 (+/− .3)	.080
Clinical features			
Renal failure	7 (63.6%)	7 (36.8%)	.150
Infection within 7 days	9 (81.8%)	13 (68.4%)	.363
CMV-Infection	2 (18.2%)	3 (15.8%)	.619
Hypomagnesemia	6 (54.5%)	3 (15.8%)	.071
Hypoalbuminemia	9 (81.8%)	17 (89.5%)	.470
Hypertension	8 (72.7%)	2 (10.5%)	.167
ECMO-therapy	8 (72.7%)	13 (68.4%)	.571
Immunological status			
Preimmunized	4 (36.4%)	2 (10.5%)	.125
Cellular rejection			
Before neurology	0 (0%)	2 (10.5%)	.510
After neurology	2 (18.2%)	5 (26.3%)	.602
Humoral rejection			
Before neurology	1 (9.1%)	2 (10.5%)	.705
After neurology	5 (45.5%)	8 (42.1%)	.493
Graft failure	1 (9.1%)	2 (10.5%)	.702
Blood transfusion			
Number of red blood cell concentrate	11.3 (+/− 10.7)	20.5 (+/− 32.4)	.620*
Number of thrombocyte concentrate	2.1 (+/− 4.0)	3.8 (+/− 5.9)	.129*
Imaging and EEG results			
Encephalopathy	*8 (72.7%)*	*4 (21.1%)*	***.008***
Vasospasm of intracranial vessels	4 (36.4%)	2 (10.5%)	.183

Abbreviations: CF, cystic fibrosis; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; EAA, exogenous allergic alveolitis; ECMO, extracorporeal membrane oxygenation; EEG, electroencephalography; IPF, idiopathic pulmonary fibrosis; PH, pulmonary hypertension.
*Mann-Whitney-U-test.

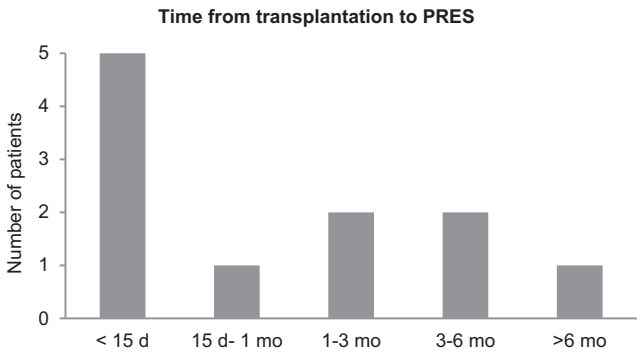

FIGURE 2 Number of patients diagnosed with PRES after lung transplantation in a time frame.

compared to patients without PRES (82% vs. 21%, $p = .002$). Other common symptoms such as headache, somnolence, neurological deficiencies, visual symptoms, and delirium were not more frequent. The maximum creatinine-level (1.9 vs. 1.1 mg/dl, $p = .047$) and the maximum TAC-level (19.4 vs. 16.5 ng/ml, $p = .048$) within 1 week prior to symptoms were significantly higher in patients with PRES. In addition, the average creatinine-clearance was lower in patients with PRES (48.9 vs. 71.5 ml/min) despite no statistical significance. Nine patients

TABLE 4 The results of univariable logistic regression for the whole study population and for the patients suspected of PRES, presenting the factors associated with the development of PRES

	OR	Beta	CI low	CI upper	*p*-value
PRES vs. no PRES in all patients					
Age in years	.92	−.09	.88	.96	***<.0001***
Male vs. female	.31	−1.18	.08	1.17	.08
CF vs. other underlying condition	10.08	2.31	2.88	35.23	***<.0001***
PRES vs. no PRES in all patients with suspected PRES					
Seizure	16.88	2.83	2.56	111.46	***.003***
Creatinine max. (mg/dl)	2.23	.80	.95	5.22	.06
Tacrolimus-level max. (ng/ml)	1.25	.22	.98	1.59	.07
Hypomagnesemia	6.40	1.86	1.16	35.44	***.03***
Hypertension	6.00	1.79	.56	63.98	.14
Encephalopathy	10.00	2.30	1.78	56.15	***.01***
Vasospasm of intracranial vessels	.21	−1.58	.03	1.39	.11

Abbreviation: CF, cystic fibrosis.

(82%) with PRES and 13 patients (68%) without PRES showed elevated inflammatory markers including leucocytes, C-reaktives Protein (CRP), and IL-6. Only two patients with PRES and three patients without PRES had CMV-infection. Other patients had bacterial, fungal or other viral infections including pneumonia, urinary tract infection, and gastrointestinal infection. A total of 81.8% of patients with PRES and 89.5% of patients without PRES had hypoalbuminemia with the same average albumin level (2.8 g/dl). The univariable logistic regression showed that hypomagnesemia was significantly associated with the risk of developing PRES (OR = 6.4, $p = .03$, Table 4). Hypertension (72.7% vs. 10.5%) was observed more frequently in patients with PRES, though without statistical significance or significant association with PRES (OR = 6.0, $p = .14$, Table 4). Only four patients (36.4%) had hypertension in their medical history. Six patients (54.5%) showed hypertension and two patients (18.2%) had severe hypertension prior to PRES. ECMO, veno-venous, or veno-arterial, was used perioperatively in 72.7% of patients with PRES and 68.4% of patients without PRES (Table 3).

2.5 | Immunological status and change of immunosuppressive regimen

All patients suspected of PRES were under immunosuppressive therapy with TAC, prednisolone, and MMF. Collectively 16 patients, all 11 PRES patients and 5 patients without PRES but with persistent neurological symptoms received CsA. Remaining 14 patients without PRES received TAC further on. After the discontinuation of TAC, patients received CsA immediately to avoid low immunosuppressant levels. After a transition period of around 1 week, the target level of CsA was achieved in all patients. There were no statistically significant differences between both groups (PRES vs. no PRES) comparing the immunological status pre- and postoperative (Table 3). In both groups, morning blood trough levels of immunosuppressive drugs were monitored regularly. There were no correlation between the average CsA or TAC-level and the occurrence of an acute cellular or humoral rejection. From 11 PRES patients, 3 patients received quadruple therapy with CsA and mTOR inhibitors (Sirolimus or Everolimus) in the further course because of progressive edema or lack of neurological improvement and two patients were put back on TAC safely after 8 and 18 months without developing PRES again. Patients in both groups received blood transfusion during and after transplantation as an immunizing event. The comparison of the number of red blood and thrombocyte concentrates showed no association between development of PRES and blood transfusion (Table 3).

2.6 | PRES imaging and EEG results

In the duplex sonography performed by neurologists, only four patients with PRES (36.4%) and two patients without PRES (10.5%) showed vasospasm of intracranial blood vessels (Table 3). Three PRES patients with vasospasm of brain vessels were successfully treated with nimodipine. After the disappearance of vasospasm in the control sonography, the treatment was terminated.

All 11 patients diagnosed with PRES showed vasogenic edema of the occipital lobe as the primary location. Other common primary locations were the parietal and the frontal lobe in seven patients (63.6%), followed by the temporal lobe in five patients (45.5%). A symmetrical pattern of cortical edema was identified in six patients (55.5%). Five patients (45.5%) only showed edema of the cerebrum. However, six patients (55.5%) had an involvement of other areas, such as the cerebellum in three cases (27.3%), thalamus in two cases (18.2%), the putamen with mid brain in one case (9.1%), the basal ganglia and the brain stem in one case (9.1%) each (Table 5). Seven patients (63.6%) received follow-up MRI, which showed complete reversibility in two cases, regressive findings in four cases and progression with involvement of new areas in one case. The patient with progressive edema also represented complete reversibility in further follow-up imaging 1 month after diagnosis. The MRI of a 53-year-old female patient with symmetrical edema in the frontal, parietal, and occipital lobes as well as the cerebellum is shown in Figure 3. One patient had a CT scan with regression of lesions, while the remaining three patients without follow-up imaging showed an improvement of symptoms.

Ten of 11 patients with PRES had an EEG to recognize any abnormal electrical brain activity. One patient showed completely normal brain activity, while eight patients showed encephalopathy of different grades, which was significantly more frequent compared to the group of patients without PRES (72.7% vs. 21.1%, $p = .008$, Table 3). Furthermore, the univariable logistic regression analysis showed a significant association between the development of PRES and encephalopathy (OR 10.00, $p = .01$, Table 4). In four patients (36.4%) we observed mild, in one patient (9.1%) moderate, and in three patients (27.3%) severe encephalopathy. Two patients (18.2%) had right occipital status and three patients (27.3%) had left hemispheric lesions, one temporal, one frontal, and one with complete left hemispheric involvement. All patients with severe and moderate encephalopathy had dissemina-

TABLE 5 Demographics, diagnostic results including MRI, duplexsonography of intracranial blood vessels, EEG, appearance of seizure as a symptom with specific therapy and clinical course of patients diagnosed with PRES

				MRI findings								
P	G	A	D	Primary locations		Secondary locations	Vasospasm	EEG	Seizure	Additional therapy	TOD	Cause of death
1	m	26	CF	occipital	left > right	cerebellum	no	right occipital status, mild diffuse encephalopathy	yes	Levetiracetam	832	Mesenterial ischemia, MODS
2	w	25	CF	parietal, occipital	left > right	–	MCA bilateral, ACA left	normal	yes	Levetiracetam, Thiopental, Nimodipine	–	–
3	w	27	CF	frontal, parietal temporal, occipital	symmetrical	–	no	right occipital status, left hemispheric lesion, severe diffuse encephalopathy	yes	Levetiracetam, Phenytoin, Topiramate, Lacosamide	826	Pleura empyema, MODS
4	w	33	CF	frontal, parietal, temporal, occipital	right > left	putamen, mid brain	MCA right > left	left temporal lesion, mild diffuse encephalopathy	yes	Levetiracetam, Nimodipine	–	–
5	m	60	COPD	frontal, occipital	right > left	–	no	left frontal lesion, mild diffuse encephalopathy	yes	Levetiracetam	134	Intestinal perforation, MODS
6	w	30	CF	frontal, parietal, temporal, occipital	symmetrical	cerebellum	MCA right > left	moderate diffuse encephalopathy	yes	Levetiracetam, Nimodipine	151	AMR, CLAD
7	w	39	CF	parietal, occipital	left > right	–	no	mild diffuse encephalopathy	yes	Levetiracetam	293	Intestinal perforation, MODS
8	w	31	CF	frontal, temporal,	symmetrical	–	–	–	no	no	–	–
9	w	40	IPF	frontal, parietal temporal, occipital	symmetrical	brain stem	MCA bilateral	severe diffuse encephalopathy	yes	Levetiracetam	–	–
10	m	67	EAA	occipital	symmetrical	thalamus	–	severe diffuse encephalopathy	yes	Levetiracetam	368	Pneumonia, MODS
11	w	53	COPD	frontal, parietal, occipital	symmetrical	thalamus, basal ganglia, cerebellum	no	severe diffuse encephalopathy, theta-delta-coma	no	no	–	–

Abbreviations: A, age; AMR, antibody-mediated rejection; CF, cystic fibrosis; CLAD, chronic lung allograft dysfunction; COPD, chronic obstructive pulmonary disease; D, primary disease; EAA, exogenous allergic alveolitis; G, gender; IPF, idiopathic pulmonary fibrosis; MCA, middle cerebral artery; MODS, multi-organ dysfunction disease; P, patient; TOD, day between transplantation and death.

tion of vasogenic edema from cerebrum to cerebellum, basal ganglia, thalamus, or brain stem. There is no correlation between the location of lesions and the dominant side of vasogenic edema. In addition, the appearance of a seizure was not related to the grade of encephalopathy or vasogenic edema. All patients with seizures received levetiracetam as anticonvulsant therapy, whereas two patients needed additional therapy with phenytoin, topiramate, lacosamide, or thiopental to terminate seizures and prevent reoccurrence (Table 5).

2.7 | Clinical course of patients with PRES

Five patients diagnosed with PRES (45.5%) were on ICU, when the first symptom appeared. From them, three patients (27.3%) had renal failure, four patients (36.4%) had clinical and laboratory signs of an infection. Five patients (45.5%) were admitted to ICU due to severe neurological symptoms such as seizures and altered level of consciousness that made intensive monitoring requisite. Only one patient with

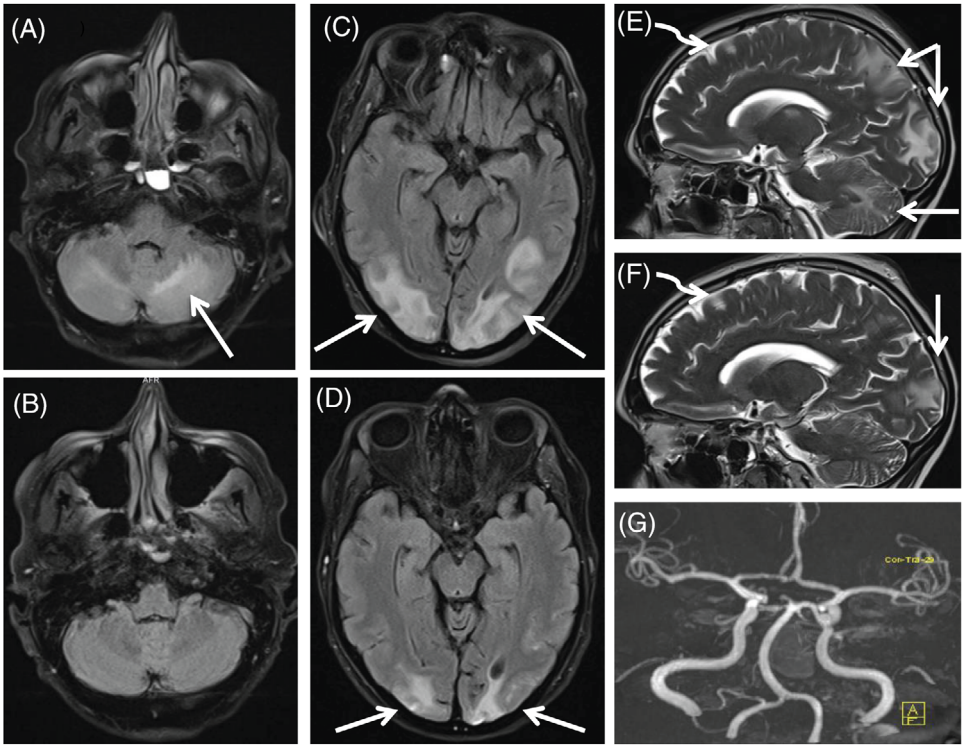

FIGURE 3 MRI of a 53-year old female patient diagnosed with PRES 9 days after lung transplantation. T2-flair MR images (A and C) in axial plain and in sagittal plain (E) show vasogenic edema of the cerebellum dominated on the left side (arrow, A and E) and bilaterally symmetrical edema of frontal (curved arrow, E), parietal and occipital lobes (arrows, C and E). T2-flair images in axial plain (B and D) and sagittal plain (F) of control MRI in 2 weeks after diagnosis demonstrate no edema of the cerebellum (B and F) and regressive findings with remaining edema in frontal (curved arrow) and occipital lobes (arrows, D and F). TOF-Angiography images (G) demonstrate the intracranial blood vessels without any vasospasm.

PRES was treated on the surgical ward. Under our treatment algorithm, all patients except from one patient with MODS, recurrent seizures, and severe encephalopathy recovered from PRES (Figure 1). Three patients with PRES (27.3%) developed a biopsy-proven minimal cellular rejection in an average time of 165 days (range, 22–297) after change of immunosuppression. In two of them and three other patients (collectively five patients, 45.5%), donor-specific HLA antibodies were detected after an average time of 160 days (range, 66–368).

2.8 | Survival

Six patients with PRES (54.5%) died of other causes, including pneumonia/pleura empyema and peritonitis, followed by sepsis and multi organ failure. One patient died because of chronic lung allograft dysfunction (CLAD) with severe respiratory failure as a result of recurring humoral rejection. In addition, two patients without PRES (10.5%) died because of pneumonia and peritonitis. The time of death (range 134–832 days after transplantation) and the cause of death were unrelated to the onset of neurological symptoms in both groups (Table 5). Seventeen patients without PRES (89.5%) and five patients with PRES (45.5%) are still alive without any remaining neurologic deficit after 40.7 months of follow-up.

3 | DISCUSSION

Neurological symptoms after transplantation are common and usually complex. Only in rare cases can the diagnosis PRES be confirmed with a therapeutic consequence. To our knowledge, there is no comparable study analyzing patient characteristics after lung transplantation and occurrence of PRES except case reports. Our cohort allowed us to study one of the largest group of patients with PRES after lung transplantation, enabling us to analyze clinical characteristics. Additionally, our study is the first one with a comparison group with similar neurological symptoms to identify the risk factors for the development of PRES.

Patients after lung transplantation frequently show postoperative neurologic complications.[37,38] In our study population of 545 lung transplant recipients, neurologic complications were common with an incidence of 28%. The incidence of PRES after SOT has been currently reported around .5%–1%[29,30] and after lung transplantation around 2%.[27,37] In our study cohort the incidence of PRES was 2% similar to literature.

The time from transplantation to the occurrence of PRES varies after SOTs. In our study group, almost half of the patients (45.56%) with PRES showed neurological symptoms within 15 days after transplantation and the average time to the onset of PRES (50.5 vs. 90 days)

was much shorter compared to current literature.[30] It was previously reported that PRES can occur at any age with a higher rate in female patients.[39] In accordance with this statement, in our study population, 73% of patients with PRES were female. Patients with PRES were much younger with the mean age of 39.2 ($p = .0002$) and it was observed more often in patients with cystic fibrosis (64%, $p = .0004$). Seizures were the most common neurological presentation of PRES (82% vs. 21%, $p = .002$) like currently described in the literature.[29,30]

Although an increase of neurotoxicity related to higher TAC levels has not always been confirmed,[29,40] the maximum TAC trough level (19.4 vs. 16.5 ng/ml, $p = .048$) was significantly higher in patients with PRES. The patients with PRES had also significantly higher maximum creatinine level (1.9 vs. 1.1 mg/dl, $p = .047$). The appearance of acute renal failure, which is again associated with PRES, could be the result of TAC nephrotoxicity. Hypertension (73% vs. 11%) and vasospasm of blood vessels (36% vs. 11%) were more frequent in patients with PRES, though without statistical significance. Vasospasm could be the result of raised endothelin concentration[41] under CNI therapy[15,16] or severe hypertension.[19] Since 64% of patients did not show any vasospasm, the reason of brain edema should be the direct toxic effect of TAC on the endothelium with the disruption of BBB and increase of vascular permeability.[14,42] The occurrence of encephalopathy of different grades in EEG (73% vs. 21%, $p = .008$) was significantly more frequent in patients with PRES. Moderate and severe encephalopathy were observed in patients with disseminated vasogenic edema including atypical areas such as thalamus, basal ganglia, and brain stem, whereas patients with brain edema of typical areas showed only mild or no encephalopathy. The most common location of brain edema was the occipital lobe (100%) followed by the parietal (64%) lobe as expected because of the affection of posterior blood circulation supplying these areas. Still, in more than half of the patients, atypical areas were involved similar to literature.[10,11]

The risk of developing PRES was significantly associated with age (OR = .92, $p < .0001$) and having CF (OP = 10.1, $p < .0001$). There was also a significant association between hypomagnesaemia and development of PRES (OR = 6.4, $p = .03$). It is known that magnesium can prohibit vasogenic edema with its vasodilatory effect.[22] Because of hypomagnesemia that appears under CNI therapy,[23,24,26] an addition of magnesium supplementation to PRES therapy might be useful as suggested by Chardain.[25]

Due to its reversible nature, all patient except from one patient with MODS showed total neurologic recovery. Almost half of the patients diagnosed with PRES (55%) died in further course (range 134–832 days) because of severe infection with sepsis and MODS or CLAD with respiratory failure. Since the cause of deaths were unrelated to PRES, there is no clear evidence for higher mortality, though the change in immunosuppression and longer ICU stay due to neurologic dysfunction could be the reason for higher infection rate with further organ damages and for the recurrent rejection.

In summary, PRES is a rare neurological disorder, which can occur under immunosuppressive therapy with TAC after lung transplantation. In case of neurological symptoms such as headache, altered consciousness, visual changes or neurological deficiencies and especially seizures, clinicians should consider PRES as a differential diagnosis and order further diagnostics, including neurological examination, EEG, MRI of the brain, and duplexsonography to confirm or rule out PRES. MRI of the brain is the gold standard to secure PRES diagnosis. Our study shows that younger patients with CF are at higher risk. We also found that higher TAC-levels, renal insufficiency and hypomagnesaemia are factors associated with PRES after lung transplantation, so clinicians should be attentive to PRES when treating patients with these characteristics.

A switch to other immunosuppressive drugs (CsA, Sirolimus, or Everolimus) should be made after secured PRES diagnosis or immediately in case of severe neurological dysfunction to improve the neurological outcome. Although it is also a CNI, CsA with lower target level can be recommended as first choice followed by a combination therapy with mTOR inhibitors. In case of progressive edema or persistent neurological symptoms under therapy with CsA[43,44] or mTOR inhibitors,[45,46] temporary discontinuation of these drugs and administration of basiliximab or belatacept as previously described in literature[27,47] may be an alternative. Since there are limited data available about the safety of these new therapy regimen, monitoring of the trough level of immunosuppressant should be intensified to minimize the risk of early allograft rejection. Also the screening for HLA antibody and transbronchial biopsy must be done more frequently to enable the early detection of rejection. After the regression of neurological symptoms, restarting TAC could be considered in case of graft failure after consulting with neurologists (Figure 1).

This study has limitations due to its retrospective design and small study cohort because of the rarity of this syndrome. Further multicenter studies with larger cohorts are required to identify independent associations in multivariable analysis.

AUTHOR CONTRIBUTIONS

Corresponding author (Gökce Yavuz), Suzette Heck, and Teresa Kauke were responsible for the study design. Robert Forbrig assessed imaging results. Gökce Yavuz, Wulf Sienel, and Julia Walter performed the statistical analysis. All authors contributed to the critical appraisal and writing of the manuscript and approved the final submission.

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CONFLICT OF INTEREST

The authors of this manuscript have no conflicts of interest to disclose as described by the *Clinical Transplantation*.

DATA AVAILABILITY STATEMENT

All primary data supporting the findings of this study are available on request from the corresponding author. These data are not publicly available due to privacy or ethical restrictions.

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