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ORIGINAL COMMUNICATION

Incidence and risk factors for seizures after heart transplantation

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Abstract Neurological complications can occur after heart transplantation and present with seizures. We examined the incidence of seizures from a population of adult patients who had received heart transplants over a period of 3 years. Brain MRI and clinical data were analysed to identify the risk factors for the seizures. Eight of the 166 post-transplant patients presented seizures (4.8%). The first seizures occurred with a mean of 30 days after the transplantation. For seven patients, the mean delay was 8 days, and for one, it was longer, 172 days. The analysis of brain MRI showed two main epileptogenic factors in the early post-transplant seizures: posterior reversible encephalopathy syndrome (PRES) due to cyclosporine treatment ($n = 4$) and cortical ischemic stroke ($n = 5$). In two patients, we identified multiple epileptogenic factors, including notably the association of PRES and cortical stroke. Since treatment of seizures in patients in the intensive care unit (ICU) after heart transplantation depends on identifying and correcting the causes, FLAIR and diffusion MRI sequences are needed, even if the patients have a previous history of epilepsy. Seizures were easy to control. In patients with PRES, imaging and clinical abnormalities improved when cyclosporine was replaced by another immunosuppressive treatment. Death of three patients was not related to seizures, but to infectious or malignant complications of immunosuppressive treatments ($n = 2$) or to post-stroke neurological deficit ($n = 1$). Mortality was similar among patients presenting seizures and those who did not.

Keywords Seizure · Transplantation · Cyclosporine · Posterior reversible encephalopathy syndrome · Cerebrovascular disease

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Introduction

Neurological complications are frequent in patients with organ transplantation, ranging from 30 to 80% of solid organ or bone marrow recipients [1]. Their frequency depends on the follow-up, ranging from 23% in the perioperative period to 81% over a follow-up of 18 years after heart transplantation [2]. Some complications are common to all types of allografts, including the direct toxicity of immunosuppressive treatment, infections and induced tumors [3, 4]. Other complications are specific for a particular type of organ transplantation. After heart transplantation these are mainly cerebrovascular disorders [1, 5–7]. The proportion of these overall neurological complications probably depends on the underlying heart disease [8]. The neurological complications can be transient or of mild severity (for example, the tremor frequently observed in patients treated with cyclosporine), or can be irreversible and severe [3]. The latter are one of

the most important factors affecting the postoperative quality of life of transplanted patients.

Previous studies have reported an incidence of seizures [2, 5, 7, 9], ranging from 1.6% [6] to 17% [8] in heart transplanted patients. As seizures can be related to various disorders, and as the medical and surgical procedures of transplantation have improved, we studied the current incidence and possible risk factors for seizures among patients with heart transplantation.

Methods

Study population and data collection

This retrospective study was based on the population of patients who underwent an orthotopic heart transplantation for a period of 3 years (from January 2002 to December 2004) at the Cardio-vascular Surgery Department, Pitié-Salpêtrière Hospital. The mean age of these patients was 44.2 years (±14.1), and the sex ratio (male/female) was 3.5. We identified the patients presenting a seizure in this population. The seizures were diagnosed based on clinical criteria. A description of the seizures is presented in Table 1. No patient was excluded, and they were all followed regularly until December 2008.

Patients underwent brain MRI and EEG in the 24–48 h after the first seizure and during the follow-up. For one patient, a CT scan was performed at the time of the seizures, and brain MRI was done 3 months later.

The arterial tension of the patient was closely monitored after the transplantation, and no patient had an episode of severe hypertension.

Immunosuppressive regimen

The immunosuppressive therapy protocol was identical for all patients. It included intravenous anti-thymocyte globulins for 5 days, intravenous (at day 2) then oral cyclosporine, oral cortisone (starting at day 4; 1 mg/kg then decrease of the dose), then mycophenolate mofetil or azathoprine (starting at day 9). The initial dose of cyclosporine was 5 mg/kg/day, then it was adjusted based on hepatic and renal function to achieve target cyclosporine levels between 200 and 300 ng/ml.

Immunosuppressive drug levels and biological parameters were monitored each day during the first weeks after transplantation, and then less frequently. Patients initially received intravenous magnesium supplementation.

Statistical analysis

Biostatistics were carried out using conventional measures of descriptions and Kaplan–Meier curves. We compared patient's characteristics with and without seizure using nonparametric association test (Wilcoxon test and Fisher test). We tested the influence of patient's characteristics on the time between the transplantation and the first seizure with log rank test. We compared the percentage of patients with seizures in our study with the percentage found in a previous study by using a chi-square test. A P-value of 0.05 was considered statistically significant. All statistical tests were two-sided. All statistical analyses were carried out using R version 2.8.0.

Results

Seizures occurred in 8 of the 166 patients (4.8%) with heart transplantation. Table 1 shows demographic and clinical data. The mean age of the patients with seizures was 34.9 (±15.8), and the sex ratio (m/f) was 1.67. The mean time between transplantation and the first seizures was 29.2 days (±57.9); the delay was 8.9 (±6.4) days for seven patients, and was longer (172 days) for another patient. Seizures were diagnosed based on generalized tonic-clonic manifestations in seven patients and visual hallucinations with confusion in the other patient. A partial onset could be identified in five patients: a limb deficit ($n = 1$), limb jerks ($n = 1$), upper visual defect ($n = 1$) and complex visual hallucinations ($n = 2$).

Brain MRI demonstrated bilateral posterior lesions in half the patients with seizures (2.4% of the overall population of transplanted patients). Lesions were hyperintense on the FLAIR sequences and mainly isointense on diffusion sequences, although some areas were hyperintense (Fig. 1). The lesions were completely reversible in three patients and showed a major decrease in the other patient. This clinically and radiologically defined syndrome is referred to as posterior reversible encephalopathy (PRES). As no other cause of PRES was found, it can be associated with the neurotoxicity of cyclosporine immunosuppressive treatment, even though this drug did not exceed therapeutic levels. In two patients, the cyclosporine related-PRES was isolated (Fig. 1). In two others, it was associated with an acute ischemic stroke (Fig. 2). Among the four patients with PRES, EEG showed slow waves in all patients and epileptic abnormalities in one.

In patients without PRES, cortical cerebrovascular complications were the most frequent cause of seizure. They consisted of focal ($n = 4$) or watershed ($n = 1$) ischemic strokes. Two of them showed a secondary hemorrhagic transformation, suggesting an embolic origin. No seizure was related to the surgical procedure (no air or fat emboli) or to brain infection.

Two patients had multiple factors for the seizures. Patient 3 already had epilepsy before the transplantation,

Table 1 Demographic and medical characteristics of patients, seizure description, imaging and EEG evaluation, treatment and follow-up

Patient	Age	Sex	Medical history	Heart disease	Time between transplantation and the first seizures	Seizures description	Brain MRI	EEG	Replacement of the immuno-suppressive treatment	Anti-epileptic drugs (initial IV drugs in parentheses)	Follow-up
1	17	F		Hypertrophic then severe dilated myo-cardiopathy	6 days	Three GTCS, preceded by right upper limb deficit	Diffuse encephalopathy, with posterior predominance	Bitemporal theta activity, mainly right	Rapamycin, associated in a second time with tacrolimus	(VPA, CLN) CBZ then LTG	One recurrence of GTCS after 3 days. Clinical and MRI improvement. Death 4 months later, due to pyocanic septicemia and primary EBV infection
2	21	M	Friedreich ataxia	Severe dilated myo-cardiopathy	12 days	Headaches, upper visual defect then 2 GTCS	Posterior encephalopathy	Posterior slowing of the background activity	Tacrolimus	(CLN) LTG	No recurrence of SZ (56 months). Disappearance of the PRES.
3	22	M	Mitochondrial disease, with epilepsy	Severe dilated myo-cardiopathy	<24 h	2 GTCS few hours after transplantation; 2 weeks later, left hemiplegia	Posterior encephalopathy and right frontal and temporal ischemia	Slowing in the right frontal and temporal lobes	Rapamycin, associated in a second time with tacrolimus	(CLN) LTG	No recurrence of SZ. Disappearance of the PRES. Partial neurological improvement. Death 1 year later, related to cutaneous and pulmonary EBV-NHL
4	42	F	Ischemic stroke at the age of 29 in the left MCA territory	Severe dilated myo-cardiopathy	16 days	2 GTCS	Posterior encephalopathy, right frontal ischemia, and left sylvian post-stroke scar	Diffuse slowing, with spikes	Tacrolimus	(CLN) VPA	No recurrence of SZ. Disappearance of the PRES. Persistence of vigilance alteration and death 4 months later
5	55	M	Diabetes mellitus, chronic renal failure	Severe dilated myo-cardiopathy	<24 h	2 GTCS, then right visual defect for 2 weeks	CT scan normal, MRI (after 3 months) normal	Diffuse slowing	No	(CLN) VPA, then LEV several months later	No recurrence of SZ (52 months)
6	51	M	Hypertension	Ischemic cardiopathy	5 months 22 days	Complex visual hallucinations, then GTCS	Semi-recent ischemic stroke in the right PCA territory	Right parietal and occipital spikes	No	(CLN) GBP	No recurrence of SZ (55 months)
7	21	M	Acute articular rheumatism	Severe dilated valvular cardiopathy	16 days	Complex visual hallucinations and behaviour abnormalities	Right parietal and occipital ischemic stroke with secondary hemorrhagic transformation	Occipital slowing with spikes	No	(CLN) VPA	No recurrence of SZ (61 months)
8	47	F	Hypo-thyroidism	Severe dilated myo-cardiopathy	10 days	Left upper limb jerks then GTCS	Bilateral watershed ischemic stroke	Diffuse spikes activity	No	(CLN) VPA	No recurrence of SZ (60 months)

GTCS generalized tonic clonic seizure, *SZ* seizure, *CLN* clonazepam, *CBZ* carbamazepine, *LTG* lamotrigine, *VPA* sodium valproate, *LEV* levetiracetam, *GBP* gabapentin, *EBV-NHL* Epstein-Barr virus-associated non-Hodgkin lymphoma

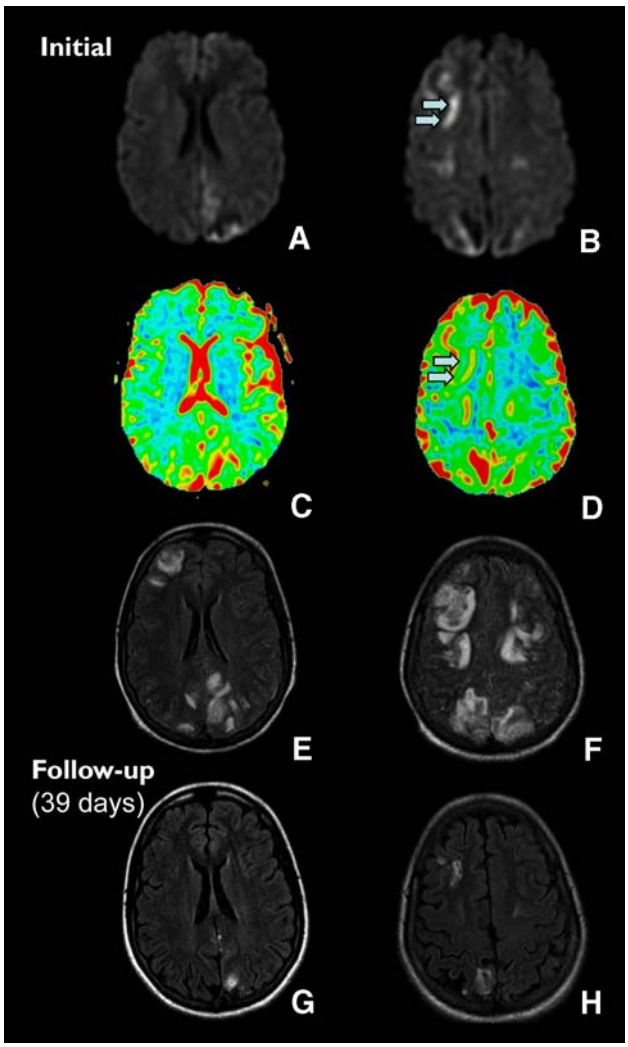

Fig. 1 Posterior encephalopathy related to cyclosporine treatment. Brain MRI in diffusion-weighted (**a**, **b**) ADC map (**c**, **d**) and FLAIR (**e**, **f**) sequences from 17-year-old patient 1, who presented seizures 6 days after heart transplantation. Multiple areas of increased signal predominating on the posterior and central region on FLAIR sequence are highly suggestive of the diagnosis of posterior reversible encephalopathy syndrome (*PRES*). Most lesions are isointense on diffusion sequence, present an increased ADC and correspond to vasogenic edema. However, some areas of hyperintense signal are present, have a normal ADC (e.g., on the right frontal gyrus, *arrow*) and correspond to a mixture of cytotoxic and vasogenic edema. The control examination performed 39 days after modification of the immunosuppressive regime (FLAIR sequence, **g**, **h**) shows the complete regression of the vasogenic lesions and the presence of persistent parenchymal destruction in the areas where cytotoxic edema was present

related to a mitochondrial disease, and presented, after transplantation, an ischemic stroke and a PRES related to cyclosporine. Patient 4 (Fig. 2) showed the same complications after transplantation and had a sequel of ischemic stroke before transplantation.

Seizures were easy to control with intravenous benzodiazepines (clonazepam 1–3 mg/day). Only one patient (patient 1) showed a recurrence of generalized tonic-clonic seizure after 3 days. They did not recur after the acute period, and the anti-epileptic drug was progressively stopped, excepted in patients with persisting brain scar.

In patients with PRES, imaging and clinical abnormalities improved when cyclosporine was replaced by another immunosuppressive treatment. Long-term prognosis was good, except for three patients, two of them with multiple factors for seizure. Death in these patients was related to infectious or malignant complications of immunosuppressive treatments ($n = 2$) or to post-stroke neurological deficit ($n = 1$).

No significant differences were found in age (age at the time of the transplantation, taken as category, $P = 0.60$), sex ($P = 0.38$) and mortality ($P = 1$) among patients with a seizure and those without seizure. We did not find clinical characteristics with significant influence on the time between the transplantation and first seizure (sex, $P = 0.29$; age, $P = 0.53$). The incidence of seizures (4.8%) in the present study was not statistically different from that of a previous study performed in our center 20 years ago [9], showing seizures in 6% of a population of 129 heart transplant adult recipients ($P = 0.89$).

Discussion

This study revealed that seizures occurred in 4.8% of adult patients after heart transplantation. High incidence of seizures (21, 26%) has been reported in infants and children with heart transplantation [10, 11]. The absence of significant difference between the incidence of seizures in the present study and that (6%) of a previous study, performed in the same center 20 years ago [9], can be related to a lack of power calculation due to the size of the populations. Finally, it suggests that in spite of improvement of medical and surgical procedures, post-transplanted patients remain at risk for seizures.

Most of the patients presented seizures with a mean delay of 8 days after heart transplantation. The two main causes of these *early* seizures were PRES related to cyclosporine and cortical stroke. We also identified several risk factors for seizure in some post-transplantation patients. In two of eight patients, three factors were identified. Since treatment of seizures in these patients depends on identifying and correcting these causes, a rapid clinical evaluation including a brain MRI and EEG is indicated.

In this study, we did not exclude the patients with a previous history of epilepsy. As illustrated by the case of patient 3, a systematic etiological evaluation should be performed in all patients with post-transplant seizures whatever their medical history.

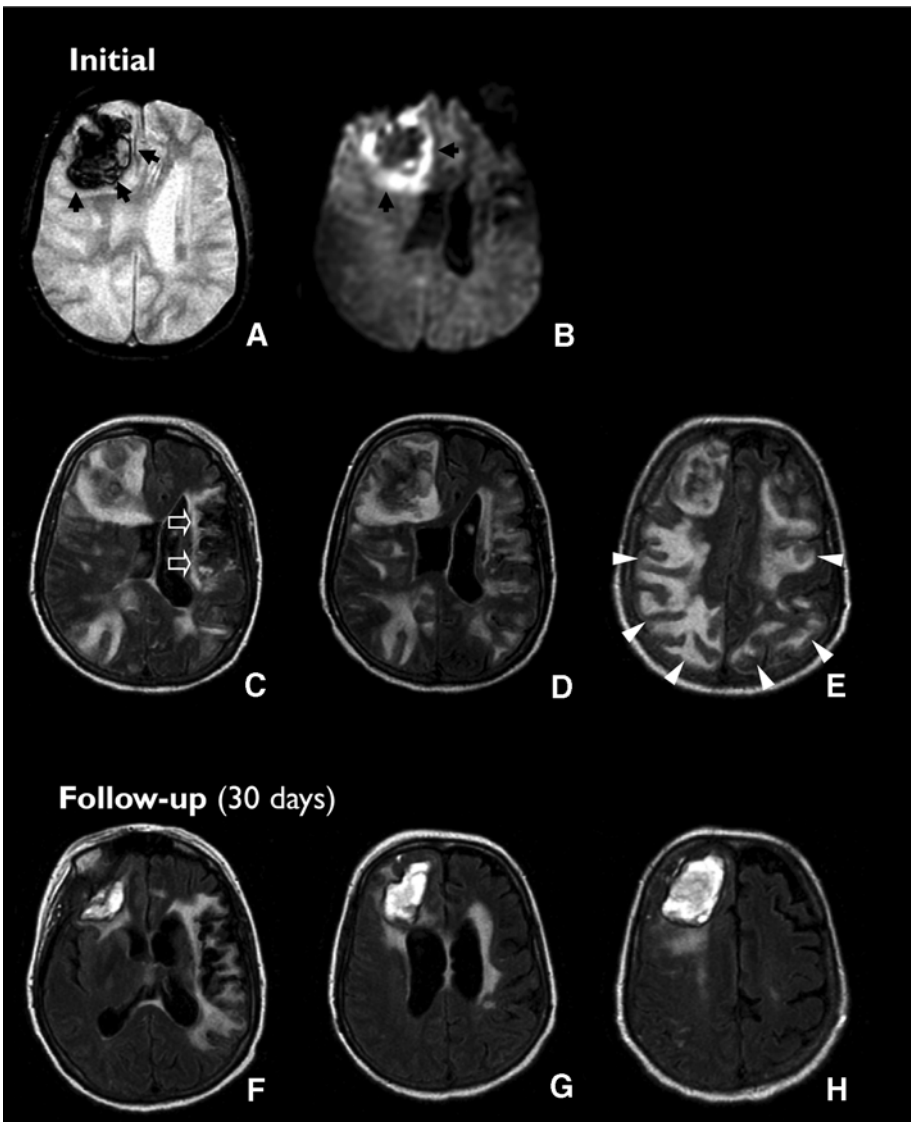

Fig. 2 Association of three cerebral lesions in a patient with post-transplantation seizures. Brain MRI in T2* (**a**), diffusion (**b**) and FLAIR (**c**–**e**) sequences from 42-year-old patient 4, who presented seizures 16 days after heart transplantation, showed (1) a recent hemorrhagic infarction in the right frontal lobe (*black arrows*), (2) the sequel of a left superficial middle cerebral artery stroke (*white arrows*) and (3) a PRES related to cyclosporine treatment (*white arrowheads*). Control examination performed 1 month later (FLAIR sequence, **f**–**h**) shows the regression of the PRES lesions and the physiological evolution of the hematoma

PRES related to cyclosporine in therapeutic ranges has become a major cause of seizures after heart transplantation. Visual manifestations are reported in 25% of the cases, altered vigilance in half of the cases, and seizures in almost 75% [12]. Brain MRI typically shows an involvement of the occipito-parietal regions, but lesions could diffuse as far as the frontal lobes. They are located both in the white matter and the cortex, the term leuko-encephalopathy being therefore not recommended. Symptoms typically reverse promptly after changing the immunosuppressive treatment. Less frequently, they are irreversible, probably due to secondary ischemic mechanisms (Fig. 1). Some data suggest that PRES related to supratherapeutic levels of cyclosporine may be reversed by reducing the drug dose [12]. Alternatively, patients might be switched to another anticalcineurin (cyclosporine to tacrolimus, or inversely), or possibly to another group of immunosuppressive drugs, such as the TOR inhibitor (rapamycin).

The pathophysiology of cyclosporine-related PRES remains unclear. It may result from a toxicity of brain endothelial cells, possibly due to elevated level of endothelin, a protein with strong vasoconstrictor actions. Potentially the predominance of PRES at posterior brain sites may be related to the lower sympathetic innervation in these regions. PRES may also be related to other changes induced by anticalcineurins, including kidney insufficiency, hypertension, hypomagnesemia, hypocholesterolemia and high doses of cortisone. It has also been reported after kidney, liver, lung and bone marrow transplantation [1, 13, 14]. The higher number of reports of PRES related to cyclosporine than to tacrolimus may be explained by the earlier introduction of cyclosporine and its more widespread present use. The incidence of tacrolimus-associated

PRES, 1.6%, in patients with bone marrow transplantation [15] is similar to that, 2.4%, in our series, in patients taking cyclosporine.

Cerebrovascular complications may result from an underlying atherosclerosis in supraaortic arteries or from the surgical procedure: perioperatoire hemodynamic failure may induce diffuse anoxia or watershed regional infarction, cardio-embolism may induce hemorrhagic infarction and anticoagulation may induce intracranial hemorrhage [1, 16].

The underlying heart disorder, such as mitochondrial disease, can also be responsible for seizure susceptibility. Other etiologies for the seizures have also been reported. Metabolic perturbations during the first postoperative days can easily be avoided by a strict biological monitoring. Opportunistic infectious or tumoral complications of immunosuppressive treatments can be revealed by seizures, but usually occurred after a post-transplantation delay higher than 6 months, contrasting with the 1 month delay in our series.

Seizures were usually associated with other neurological signs, but they were the most prominent symptom in patients hospitalized in post-surgical ICU. Most of the patients presented with secondarily generalized seizures ($n = 7$). A visual aura was the most frequent symptom preceding these seizures ($n = 3$) and could be related to PRES as well as to stroke in the posterior territory.

In conclusion, seizures occurred in 4.8% of our cohort of adult patients with heart transplantation and were related to two main causes: PRES related to cyclosporine treatment and cortical ischemic stroke. In all patients, seizures were easy to control, as previously reported [17]. Perioperative strokes were recently reported as the most important neurological complication affecting survival after heart transplant [2]. The two patients with multiple factors for seizure had compromised long-term prognosis; the small size of this subgroup did not allow statistical analysis, and therefore additional data are needed to identify prognostic factors.

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