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Neurological examinations after liver transplantation concerning patients under corticosteroid immunosuppression and either FK506 or cyclosporin

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Abstract To study the neurological sequelae in liver transplanted recipients, 25 patients were followed up between 5 and 30 months after transplantation and another 14 patients were seen before and after transplantation. Physical examination took special note of tremor and polyneuropathy; additionally, patients estimated concentration and memory, tremor, paraesthesias and sleep disturbances on a self-rating scale. Tremor was reported to be preexistent in 50% of the later FK506 and cyclosporin group and only temporarily rose afterwards. Twenty-eight percent complained of tremor and 20% said that it interfered mildly with daily activity. Only 2 of 39 patients showed new signs of polyneuropathy. Concentration and memory improved significantly after transplantation. In the second group of patients, MRI, EEG, lumbar puncture and neuropsychological tests were done just before and routinely after transplantation, revealing numerous preexisting neurological deficits with only singular changes afterwards.

Key words FK 506 and neurological side-effects
Liver transplantation

Introduction

A number of neurological side-effects seen in liver transplant recipients treated with cyclosporin A seem to occur also under FK506 immunosuppression. To compare the more frequent neurological complications seen with FK506 and cyclosporin i.e. tremor, paraesthesia, mental disturbances and cerebrovascular lesions, two transplant populations were followed up.

The first group ($n = 25$) was regularly seen 5–30 months after transplantation. The second group ($n = 14$) was additionally examined before and at different times after transplantation with EEG, MRI, lumbar puncture and neuropsychological tests in order to determine preexisting morbidity.

Methods

The 39 adult patients underwent orthotopic liver transplantation for various liver problems. In group 1 (25 patients) these were as follows: chronic hepatitis with cirrhosis (10), primary biliary cirrhosis (4), cystic degeneration (2), Budd-Chiari syndrome (2) and in one patient each, primary sclerosing cholangitis and hepatocellular carcinoma. In group 2 (14 patients) the reasons for transplantation were: chronic hepatitis with cirrhosis (3), Budd-Chiari syndrome (3), primary biliary cirrhosis (2), cystic degeneration (2) and primary sclerosing cholangitis (1).

Group 1

In group 1, the median age was 41 years (mean age was 45.4 years) at the time of liver transplantation and follow-up ranged between 5 and 30 months. Eighteen patients received FK506 treatment with an initial dose between 0.05–0.30 mg/kg body weight (bw) per day p.o.

and then the dose was adjusted to maintain plasma levels of 0.3–3.0 ng/ml. Seven patients were treated with cyclosporin A, ranging between 100 mg and 325 mg p.o. daily.

Physical examination took special note of the character of tremor and peripheral neuropathy. In addition, patients were asked to estimate their concentration and memory, tremor, paraesthesia and sleep disturbances on a self-rating scale.

Group 2

In group 2, the median age at the time of transplantation was 52 years (mean age was 49.3 years). Seven patients were treated with FK 506 as in group 1 and the other seven were treated with cyclosporin in common doses. All patients were seen 6 h before transplantation and again on days 3, 8, 28 and 180. Before transplantation, all patients in group 2 underwent neurological examination and neuropsychological tests consisting of Mini Mental State, Recurring Figures Test (KIMURA) and Mosaic Test (HAWIE), which were repeated on day 180. EEG lumbar puncture and MRI were done before and again after transplantation as far as clinical condition allowed. Three patients on cyclosporin and one on FK 506 died before day 180.

Results

Group 1

Nearly all 18 patients on FK 506 treatment received a similar dosage, 6–8 mg per day; 4 patients received less (4–5 mg) and 2, more (9 mg). The dose of cyclosporin varied from 100 mg to 325 mg/day. In the FK 506 subgroup, four patients had no tremor, nine had slight tremor and only five had definite tremor, three of whom were converted from cyclosporin previously. Of those on cyclosporin treatment, two had no tremor, two had mild temor and three had a definite tremor. Within this small range of dosage, there was no correlation to severity of tremor. Two patients on cyclosporin had, in addition, an intention tremor. In respect to preoperative self-rating, 44% of FK 506- and 43% of cyclosporin-treated patients had preexisting tremor, with possible or slight tremor in 77% and 71%, respectively, but tremor was only disturbing in 28% and 29%, respectively. It was reported to be dose-dependent in 55.5% and 57.1%, respectively, and was expecially noticed within the first 2 months after transplantation (Fig. 1).

Signs of mild clinical polyneuropathy were present in one patient treated with FK 506 and two patients treated with cyclosporin. Paraesthesia preexisted in one patient and had no clinical correlate in another patient.

According to self-estimates in the FK 506 group, concentration improved in eight of ten patients (80%) with former disturbed function (10 patients; 55.5%). It remained the same in eight patients (44.5%) and was reported to worsen in one. In the cyclosporin subgroup, there was no difference reported compared to the preoperative state (Fig. 2). Memory, too, was reported to improve in seven (87%) of eight patients with a former disturbance (44.5%) on FK 506 treatment, nine (50%) remained unchanged and one worsened. Two of the cyclosporin-treated recipients (66%) noticed better memory function compared to the preexisting state (Fig. 3).

Eight patients in each subgroup complained of sleep disturbances especially before transplantation. After-

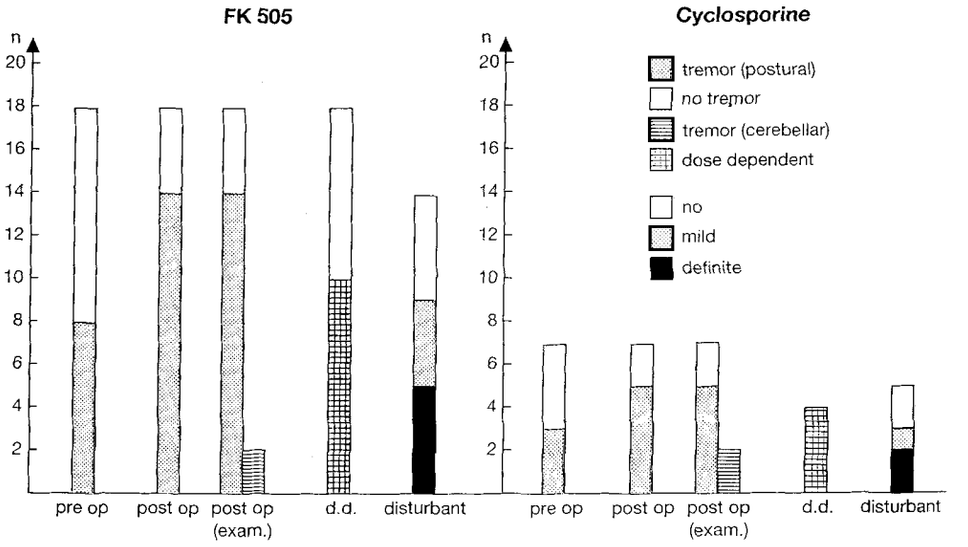

Fig. 1 Tremor within 30 months on FK 506 (18) versus cyclosporin (7) treatment (*d.d.* dose dependent)

Table 1 Perioperative neurological examination and complications ($n = 14$, *FK* FK 506, *Cy* Cyclosporin)

Day	TREMOR				Rigor		Dysdiadochikinesis		Ataxia		Paratetraparesis		Myoclonism		Anarthria		Dysarthria		Seizures		Confusion apathy		Coma		Visual disturbance		Mild signs of polyneuropathy			No neurological disturbance	
	Posture		Calm																												
	FK	Cy	FK	Cy	FK	Cy	FK	Cy	FK	Cy	FK	Cy	FK	Cy	FK	Cy	FK	Cy	FK	Cy	FK	Cy	FK	Cy	FK	Cy	FK	Cy	Dead			
0 before Transplantation	5	3	2	2	1	1	1	1	4	3			1				1										1	2				4
3		5	5	1	0	2	1		1	1	1		1	1	1			2	1			1	1		2		1				2	1
8	4	2	1		1	1	1	1	1		1	1	1	1	1	1	1	1	2	3		3	1	1							2	1
14					1		1		2		1	1	2		1		1				1	1	1	3							2	1
28	2						1		2		1	1	2	1	1		1			1		2	1	2					+	2	3	1
160	(5)	(3)			1		1		1																				+	$^1/_1$		

Frequent complications

	TREMOR										Anarthria		Dysarthria		Seizures		Confusion apathy		Coma			Mild signs of polyneuropathy		
	Posture		Calm																					
	(%)		(%)								(%)		(%)		(%)		(%)		(%)			(%)		
	FK	Cy	FK	Cy							FK	Cy	FK	Cy	FK	Cy	FK	Cy	FK	Cy		FK	Cy	
0	71	43	29	29																		14	29	
3	71	71									14	14	14	14	29	43	29	57	14	71				
160	71	43	0	0																			29	

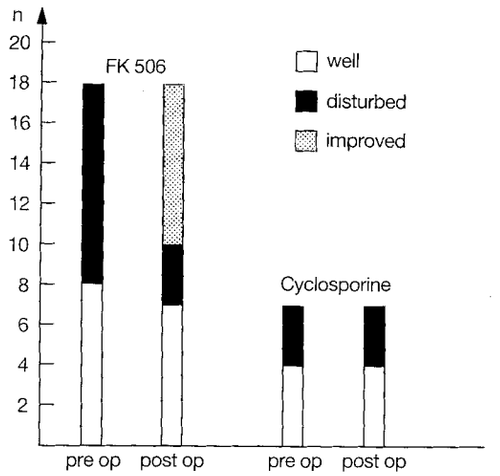

Fig. 2 Self-reports on concentration before and after transplantation by patients on FK 506 and cyclosporin

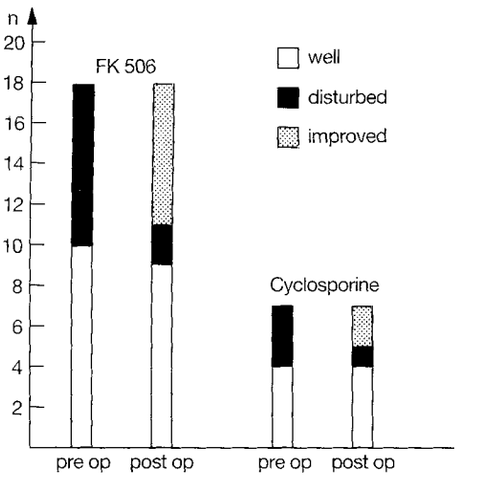

Fig. 3 Self-reports on memory before and after transplantation by patients on FK 506 and cyclosporin

ward transplantation, only one patient in each subgroup suffered from persistently disturbed sleep; one FK 506 recipient noticed sleep disturbance because of headache.

Group 2

Special regard was again taken to tremor, which preexisted in eight patients (57%; Table 1). After transplantation, the finding were similar; 71% (5 patients) of FK 506- and 45% (3 patients) of cyclosporin-treated patients had tremor. There was only one patient, in the cyclosporin group, who developed a new tremor. Previously noted basal ganglia tremor, on the other hand, disappeared. Other extrapyramidal functions (rigor, diadochokinesis) were less affected in both groups. Dysaesthesia, with mild signs of polyneuropathy, was noticed on three occassions before and only twice 6 months after transplantation in the cyclosporin subgroup.

Other complications during the perioperative phase were confusion/-apathy, coma, seizures, dys-/anarthria, myoclonisms and central paresis. Confusion/apathy, coma and seizures occurred more often with cyclosporin treatment, while central paresis and anarthria/dysarthria were similar. Three patients on cyclosporin treatment died within 5 weeks and one patient on FK 506 medi-

Table 2 Current MRI findings

MRI	Day 0	Day 8		Day > 30	
		Identical	New	Identical	New
Normal	3				
Unspecific ischaemic/vascular spots	6	4		2	
Basal ganglia lesions (T1 signal intensity)	7	4		2	
Sub-/cortical atrophy	4	1		1	
(Extra-) Pontine myelinolysis	0				1
Haemorrhage	0		1		
	0				
Infections	0				1 Abcess
	$n = 13$	$n = 7$ not done = 4, dead = 2		$n = 5$ not done = 4, dead = 4	

Table 3 Cerebrospinal fluid before transplantation

Diagnosis	Cytology	Oligoclonal bands	Identical band	Blood-brain barrier disturbed	*n*
Posthepatitic cirrhosis	Normal	No		1	3
and Hepatocellular carcinoma	Normal	②	③	②	3
Budd-Chiari syndrome	Normal	No	1	No	2
PBC	Normal	No	1	No	1
Cystic degeneration	Normal	No	1	1	2
PSC	Normal	No	1	No	1

cation died after 4 months from systemic nocardious infection. On the other hand, one severe pontine myelinolysis, which only slowly improved, occurred with FK 506.

MRI (Table 2) done 1 h prior to transplantation also disclosed preexisting abnormalities concerning basal ganglia hyperintensities (T_1 weighted; seven patients), white matter lesions (six patients) and (sub-) cortical atrophy in 77%, 54% with typical signs of hepatic encephalopathy. The follow-up MRIs showed no significant changes with the exception of one haemorrhage and central pontine myelinolysis.

Cerebrospinal fluid also showed preexisting abnormalities presenting as identical bands, thus, indicating a systemic immunological disorder in various liver diseases. We found them especially in hepatocellular carcinoma with additional oligoclonal bands (Table 3).

The neuropsychological examination showed clear improvement in orientation, attention, memory and calculation after transplantation, tested with Mini Mental State (Fig. 4). Similar improvement was noted in the Mosaic Test, with a mean preoperative mistake ratio of 1.2 and 0.7 after transplantation. The more difficult test of "Recurring Figures" showed a slight but not significant intraindividual improvement except for three patients (Fig. 5).

Discussion

Compared to cyclosporin A, FK 506 has proved to be more effective in preventing and treating organ rejection [1, 2] and is said to evoke less hypertension [3, 4] as well as fewer lesions and infections of the central nervous system [5]. Nevertheless, a number of neurological complications are reported during the postoperative phase [4–9] that can be divided into major (akinetic mutism, seizures, psychosis, focal deficits, movement disorder) and minor (tremor, headache, sleep disturbances, dysasthesia) side-effects as observed by Eidelman et al. [6]. They studied

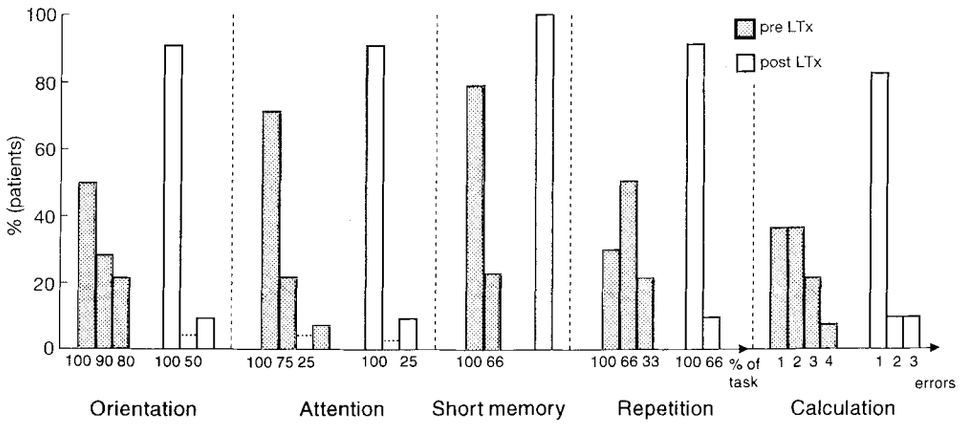

Fig. 4 Results of Mini Mental State performed before and after liver transplantation (LTx)

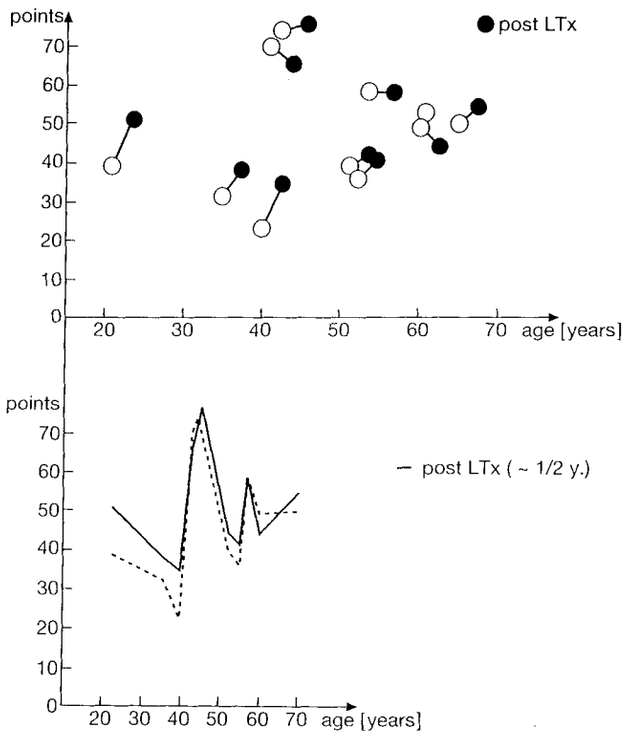

Fig. 5 Results of Recurring Figures test performed before and after LTx

238 liver transplant recipients where akinetic mutism and seizures were the most frequent major side-effects and tremor and sleep disturbances were the most common so-called minor side-effects. Generally they occurred during the early postoperative phase (30 days), were said to improve after FK 506 levels declined, did not reappear in cases started on FK 506 again and were seen less with other organ transplantations [3, 4].

Side-effects with FK 506 do not generally differ from those described with cyclosporin therapy [5, 6, 10–17], even observed in the same patient [7]. They do not correlate simply to primary liver disease, duration of illness or age of recipient.

We emphasized in this study that similiar neurological deficits that are described postoperatively as a result of long-term – and acute – liver failure with individual susceptibility to metabolic and circulatory disturbances and medications [18–21].

In both groups, tremor preexisted (50% and 44% in groups 1, 2, respectively, with a positive correlation (including other extrapyramidal disorders) to preexisting basal ganglia lesions (MRI) in 77.8%, and mostly with a higher-frequency (about 8–10 Hz) than Parkinson's tremor or flapping tremor. The primary increase in tremor postoperatively lessened with lowering FK 506 or cyclosporin A. It seemed that the FK 506 tremor was only less intense than the cyclosporin-induced one. Mild signs of peripheral neuropathy were seen only once with FK 506 and twice with cyclosporin and had preexisted in one patient. There was no correlation to the sometimes observed painful dysaesthesia within the 1st weeks after transplantation. Headache and sleep disturbances were only complained of by 2 of 39 patients.

The neuropsychological tests revealed significant improvement after transplantation with improved Mini Mental State and Mosaic Test but only a small improvement in more difficult tests (Recurring Figures), indicating a preexisting metabolic encephalopathy in almost all patients [18, 20, 22].

Finding of routinely done MRI supported the presence of neurological deficits presenting as basal ganglia and white matter (vascular) lesions without additonal cerebrovascular lesions in eight of nine patients. With the exception of one patient, we did not observe signs of vascular lesions (focal necrosis of the media and adventitia of arteries) as described in experimental animals and a few autopsied humans [9, 23]. Neuropathological findings of 28 liver-transplanted recipients, comparing CNS lesions in patients on FK 506 and cyclosporin treatment have revealed no focal or generalized necrosis of cerebral vessels [5]. One patient on FK 506 developed pontine myelinolysis, supported by MRI, and only slowly recovered with remaining deficits. He and three other patients without MRI-changes also had expressive dysarthria progressing to anarthria with nearly complete relief [4, 6, 8]. Two of them were on FK 506 and two were on cyclosporin treatment. Cerebrospinal fluid also reflected preexisting morbidity with immunological signs presenting as oligoclonal bands and identical bands in CSF and blood. Oligoclonal bands were only represented in patients with hepatocellular carcinoma; otherwise, there was no correlation to primary liver disease.

In conclusion, we estimate the following:

1. That the FK 506 tremor is dose-dependent, with a similar frequency to the cyclosporin-induced one, but is less intense and is not the consequence of peripheral neuropathy
2. That mental disturbances improve after transplantation without signs of FK 506 neurotoxicity
3. That numerous postoperative neurological abnormalities preexist and are influenced by metabolic disturbances and medical background

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