Chronic Parkinsonism Associated with Liver Cirrhosis

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OBJECTIVE: To prospectively study parkinsonism prevalence in patients with liver cirrhosis of various causes and establish correlations between cirrhosis severity and parkinsonism, neuroradiological and biological findings.

BACKGROUND: Cirrhosis-related parkinsonism represents a unique subset of acquired hepatocerebral degeneration. Disorder prevalence and natural history after transplant remains largely uncertain.

METHODS: A prospective study of 120 patients with liver cirrhosis recruited from the liver transplant list at Lahey Clinic, Burlington, MA (Table 1). Each patient underwent Unified Parkinson's Disease Rating Scale (UPDRS) testing, standard liver transplant evaluation and repeat testing pre-transplant and at 6 weeks, 3 and 12 months post-transplant. Patients with parkinsonism also underwent brain MRI pre- and 1 year post -transplant. Correlation was measured between MELD severity and motor part UPDRS, copper, ammonia, manganese, and iron levels and signal MRI changes.

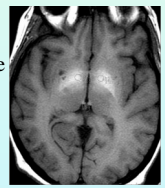
Table 1. Demographics

	Parkinsonism n=62	No Parkinsonism n=58
Gender	37 M 25 F	46 M 12 F
Mean Age, *y*	55.5 (*range* 38-68)	54.2 (*range* 20-69)
Disease Category *Mixed= multiple diagnoses* *Alcohol= alcoholic cirrhosis* *Viral= Hepatitis* *Other= PCS, etc*	27 Mixed 15 Alcohol 10Viral 10 Other	26 Mixed 12 Other 11 Viral 9 Alcohol
Disease Duration, *y*	8.4 (*range* 0.6-30)	6.0 (*range* 0.1-20)
Mean MELD	14.4	14.0
Manganese, *UG/L*	18.55	16.98
Ammonia, *UMOL/L*	59.7	Not Done
Copper, *UG/DL*	95.7	Not Done
Iron, *UG/DL*	118.4	103.2
UIII (Motor) Total	15.2	0
UPDRS (U) Total	28.6	10

We also performed a sub-study in which brain MRI of the patients with hepatocerebral degeneration (HCD) were blindly evaluated with a matched cohort of patients with Parkinson's Disease (PD). T1 weighted brain MR ratios were obtained from symmetrically placed standardized (25 mm²) regions of interest (ROIs) within the medial globus pallidus versus thalamus versus forceps minor white matter in an effort to normalize for minor variations in the T1 pulse sequence, equipment/ coil enhancements & head positioning over the 5 year prospective time interval. Ratios of right (R) and left (L) medial globus pallidus/thalamic (thal) and medial globus pallidus/white matter (WH) were calculated and subsequently correlated with clinical metrics.

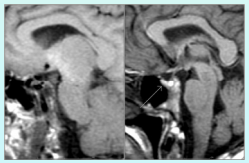
The ROIs for the medial globus pallidus were positioned symmetrically on the right and left, just posterior to the anterior commissure and 10mm off midline (Fig 1).

Figure 1



Signal intensity within the adenohypophysis on sagittal T1 weighted imaging was considered elevated if its signal intensity was equal to or greater than that of the corpus callosum (Figure 2).

Figure 2



RESULTS: BIOLOGICAL: Out of 120 patients, 62 (52%) exhibited parkinsonism (Table 2). In the parkinsonian group (HCD), we found no correlation between severity of MELD and motor part UPDRS (p=0.71) and no correlations were found with copper (p=0.36), ammonia (p=0.86), manganese (p=0.90) or iron levels (p=0.30). There was also no correlation with type of cirrhosis and total motor UPDRS (UIII). No differences were seen between the 2 groups (HCD vs. non-parkinsonism) in mean manganese (18.55 vs. 16.98; p=0.39). Mean iron level was found to be higher in the group with parkinsonism, representing a slight trend (118.4 vs. 103.2, p=0.10).

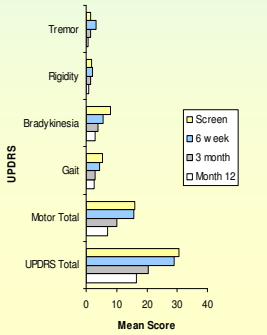
PARKINSONISM: Nineteen patients with parkinsonism (HCD) underwent liver transplantation (Figure 3). Statistical analysis was performed using paired t-tests ($p \leq 0.05$). At **6 weeks** post-transplant no statistically significant changes were seen, although clinical improvement was noted in bradykinesia, gait and total UPDRS. At **3 months** post-transplant, statistical significant improvement was seen in bradykinesia (p=0.02), gait (p=0.001), UIII (p=0.02) and total UPDRS (p=0.03). No statistical differences were noted in tremor (p=0.75) or rigidity (p=0.93), although slight clinical improvement was seen. At **1 year** post-transplant 16/19 were re-evaluated. Statistically significant improvement was found in bradykinesia (p=0.001), gait (p=0.005), UIII (p=<.0001), and total UPDRS (p=0.002) and clinical improvement in tremor (mean score 1.6-0.7) and rigidity (mean score 1.7-0.8).

Table 2. Percentage of HCD patients (n=62) with parkinsonism symptoms (individual UPDRS motor questions ≥ 1)

Abnormal Motor Scores	%*
Tremor, *Symptomatic complaint*	73
Rigidity	
R Upper	60
L Upper	68
Bradykinesia	
R finger taps	68
L finger taps	77
R hand movements	68
L hand movements	84
R leg agility	66
L leg agility	63
Arising from chair	60
Gait	68
Postural stability	76
Body bradykinesia/hypokinesia	84

(*motor abnormalities seen in ≥ 50 % of patients are reflected)

Figure 3. Mean motor UPDRS scores from each evaluation time point in patients with parkinsonism (HCD) pre & post transplant (n=14)



NEUROADIOLOGICAL and SUB-STUDY: Basal ganglia hyperintensity was seen in all pre-transplant images, resolving 1 year post transplant (n=14). Increased pituitary T1 signal was seen in 59% of the HCD group pre-transplant compared to only 7% in the PD group (chi square; p=<0.0001) and resolved post-transplant. No differences were noted between the HCD group 1 year post-transplant and the PD group (p=0.85). Although motor UPDRS was not statistically correlated (p>0.05) with any of the four MRI parameters (R/L Thal or R/L WH) pre- (n=47) or 1 year post-transplant (n=14), all correlations were positive. Larger drops in MRI ratios were associated with larger drops in motor UPDRS (Figure 4). The absence of significance is suspected due to the rather small sample size.

There were statistical differences seen between the pre transplant HCD group (n=47) and PD group (n=32) in the following: R/Thal (p<0.0001); L/Thal (p<0.0001); R/WH (p=0.05) and L/WH (p=0.004). A difference was found in transplanted HCD patients1 year post-transplantation (n=14) vs. the PD group (n=32) in the L/Thal (p=0.007). Significant improvements were also seen in the MRI ratios from pre-transplant to 1 year post-transplant in the 14 transplanted HCD patients (R/Thal p=<.0001; L/Thal p=0.0007; R/WH p=0.008; L/WH p=0.02).

Figure 4. Change in UIII and MRI ratios post transplant

Variable	N	Mean	Std Dev	Sum	Minimum	Maximum
UIII_total	14	-8.78571	4.90178	-123.00000	-16.00000	-1.00000
rat_R/Thal	14	-0.22488	0.14496	-3.14832	-0.41528	0.07255
rat_L/Thal	14	-0.20184	0.17085	-2.82570	-0.45952	0.09804
rat_R/WH	14	-0.14420	0.17074	-2.01876	-0.53733	0.13151
rat_L/WH	14	-0.12140	0.16452	-1.69962	-0.44191	0.18156

Pearson Correlation Coefficients *(p-values)*

	rat_R/Thal	rat_L/Thal	rat_R/WH	rat_L/WH
UIII_Total	0.20869 *0.4740*	0.13494 *0.6456*	0.30806 *0.2839*	0.08148 *0.7819*

CONCLUSIONS: Our study demonstrates a high incidence (52%) of parkinsonism in patients with liver cirrhosis. Parkinsonism symptoms consisted mostly of tremor, rigidity, bradykinesia and gait/balance difficulties. No correlations were found between type or severity of liver cirrhosis (MELD), manganese, ammonia, copper or iron levels and parkinsonism severity measured by UPDRS. Statistically significant improvement was found in motor and total UPDRS scores, gait and bradykinesia 1 year post-transplant with noted clinical improvement in tremor and rigidity. Patients with cirrhosis and parkinsonism had statistically significant MRI biomarkers (T1 basal ganglia hyperintensity), compared to patients with PD, resolving post-transplant. Positive correlations were also noted between motor UPDRS and MRI ratios, though did not reach statistical significance most likely due to small sample size. Our study remains ongoing until all patients have been transplanted but is so far suggestive that parkinsonism severity in liver cirrhosis may improve after transplantation.

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