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Neurodegeneration in Hepatic and Neurologic Wilson Disease

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Summary: Clinical presentation of Wilson disease (WD) includes hepatic and neurologic manifestations. This study compares subcortical brain regions by magnetic resonance imaging (MRI) in WD patients with and without neurological symptoms. Distinct atrophy affecting the basal ganglia, accumbens and hippocampus were present in neurological WD. Cerebellar atrophy was observed in hepatic WD without neurological symptoms.

Main Text: Wilson disease (WD) is associated with recessive variants in *ATP7B*, which encodes a copper-transporting ATPase, causing insufficient copper incorporation into ceruloplasmin and reduced biliary copper excretion. Clinical presentation of WD is heterogeneous and includes hepatic and neurologic manifestations(1). A recent study has demonstrated that age and sex but not genotype are associated with clinical presentation(2).

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To study if the degree and patterns of neurodegeneration differ between hepatic and neurologic WD, a cohort of patients was studied with cerebral magnetic resonance imaging (MRI) and images subjected to automated segmentation of subcortical brain regions. A cohort of 20 patients with WD (Leipzig score ≥ 4) from whom MRI of the brain was available were included (Figure S1). For further analysis patients were hierarchically grouped into neurologic or hepatic WD according to clinical manifestation. Patient characteristics including details on liver disease stage and neurological impairment quantified by the Unified Wilson Disease Rating Scale (UWDRS)(3) are shown in Table 1. Patients with neurological symptoms were classified as neurological regardless of coexisting liver disease. Patients with hepatic WD had no neurological impairment.

Normalized volume estimates revealed significant reduction in multiple subcortical brain regions of patients with WD (Table S1). Compared to age and sex-matched healthy controls, signifcant subcortical volume loss was evident in the accumbens area, amygdala, caudate, cerebellar cortex and white matter (WM), hippocampus, middle cerebellar peduncle (MCP), pallidum, putamen and the superior cerebellar peduncle for both hepatic and neurological WD ($P < 0.05$; Figure 1, Table S2). The volume of the pons and thalamus were significantly reduced only for hepatic WD.

When neurological WD patients were compared with hepatic WD patients significant reductions of regional brain volumes were observed in the putamen and caudate nucleus of the former ($P < 0.05$; Figure 1 and Table S2).

Observer-independent volumetric MRI analysis revealed widespread subcortical volume loss of the pallidum, putamen, cerebellar WM and the accumbens area being most severely affected in WD. Our findings are in line with recently published studies that revealed extended subcortical atrophy with basal ganglia involvement in patients with neurologic WD(4). Interestingly, the patterns of subcortical atrophy differed in hepatic and neurological WD with predominant affection of the cerebellar white matter compartment in the former and basal ganglia involvement in the latter. The results indicate that cerebellar atrophy is evident in hepatic WD without neurological symptoms and suggests that the magnitude of striatal atrophy might herald transition from hepatic to neurologic WD.

At present, the pathomechanism responsible for this phenotypical heterogeneity is unknown and requires confirmation in larger prospective studies. In addition to the low

number of patients, another potential limitation of the present study is that patients were investigated median 12.5 years after diagnosis, after which pharmacological treatment had been initiated in all but one hepatic WD patient who underwent liver transplantation shortly after MRI. A potential effect of treatment on subcortical volumes can therefore not be excluded. Recent studies have shown qualitative or semi-quantitative MRI differences when comparing hepatic and neurologic WD. We objectively quantified volumes of the subcortical brain regions and compared results with age- and sex-matched controls which may be independent of changes in previously reported signal intensities(5).
Our finding of subclinical volume loss of subcortical brain regions in hepatic WD supports early diagnostic cerebellar MRI to improve disease staging and tailoring the appropriate treatment.

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Table 1: Patient characteristics

	All patients (n=20)	Hepatic WD (n=13)	Neurologic WD (n=7)	*P*
Female, n (%)	8 (40)	3 (23)	5 (71)	0.06
Age at onset, years	18 (13 – 22)	16 (13 – 23)	19 (14 – 24)	0.79
Age at diagnosis, years	21 (14 – 30)	18 (13 – 30)	25 (19 – 30)	0.82
Ceruloplasmin, mg/dl	6.4 (2.4 – 14.2)	8.6 (2.6 – 15.4)	2.7 (1.9 – 11.7)	0.29
Kayser-Fleischer ring, n (%)	6 (30)	2 (15)	4 (57)	0.05
Urin copper, µg/24h	328 (219 – 759)	327 (162 – 737)	329 (256 – 825)	0.60
Hepatic copper, µg/g	832 (166 – 914)*	832 (166 – 882)**	946 (502 – 1390)***	0.38
***ATP7B* mutations, n (%)**				0.86
H1069Q homozygote		1 (8)	0 (0)	
other homozygotes		1 (8)	2 (29)	
H1069Q compound		2 (15)	1 (14)	
other compound		4 (31)	1 (14)	
only H1069Q		2 (15)	1 (14)	
only other		2 (15)	1 (14)	
unknown		1 (8)	1 (14)	
Fibroscan, kPa	9.9 (6.8 – 16.4)†	8.1 (6.7 – 16)††	12.0 (6.5 – 23.1)†††	0.50
MELD score‡	9 (8 – 11)	9 (8 – 17)	9 (8 – 11)	1.0
UWDRS score	0 (0 – 33)	0 (0 – 0)	27 (10 – 33)	< 0.001
Treatment, n (%)				0.52
D-pencillamin	10 (50)	7 (54)	3 (43)	
Trientine	5 (25)	3 (23)	2 (29)	
Zinc	4 (20)	2 (15)	2 (29)	
Treatment duration, years	12.5 (1 – 16)	14 (3 – 18)	10 (0 – 16)	0.26
Cirrhosis, n (%)	11 (55)	8 (62)	3 (27)	0.42
Liver transplantation, n (%)	3 (15)	2 (15)	1 (14)	0.95
T1 hyperintensity in basla ganglia n (%)§	2 (10)	0	2 (29)	0.06

Data are given as n (%) or median (25th percentile – 75th percentile)

UWDRS, Unified Wilson Disease Rating Scale

*n=7, **n=5, ***n=2 (range), †n=18, ††n=11, †††n=7

‡MELD scores are only reported for patients with cirrhosis

§Symmetric T1 hyperintensity in the globus pallidus and substantia nigra was present in 2 patients.

Figure Legend:

Figure 1 (A) Subcortical volumetric data expressed as z-scores for specified subcortical brain regions in patients with hepatic (full circles) or neurologic WD (open circles). Regional medians for each group are marked by horizontal lines. The dashed line at a z-score of -2.0 serves as a visual reference for severe atrophy.
WM: white matter, MCP: middle cerebellar peduncle, SCP: superior cerebellar peduncle. The marks (*) indicate statistically significant differences between hepatic and neurological WD. (B) Individual T1-weighted 3D magnetization-prepared rapid gradient echo image of representative patients with hepatic WD, neurological WD, and a healthy participant and superimposed segmented areas of the caudate (turquoise), putamen (pink), globus pallidus (blue), thalamus (green), cerebellar gray matter compartment (orange), cerebellar white matter compartment (yellow). Marked volume reduction can be inferred from smaller coloured areas in the cerebellar white compartment and the cerebellar cortex from both WD patients. In addition, the areas representing the putamen and the caudate of the patient with neurological WD are markedly reduced as indicator of significant volume reduction in the respective brain regions. The area of the MCP overlap entirely with the cerebellar white matter compartment as part of it and hence was not separately delineated.