HEPATOLOGY

CLINICAL OBSERVATIONS IN HEPATOLOGY | HEPATOLOGY, VOL. 74, NO. 2, 2021

Neurodegeneration in Hepatic and Neurologic Wilson's Disease

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Clinical presentation of Wilson disease (WD) includes hepatic and neurologic manifestations. This study compares subcortical brain regions by magnetic resonance imaging in patients with WD and without neurological symptoms. Distinct atrophy affecting the basal ganglia, accumbens, and hippocampus was present in neurological WD. Cerebellar atrophy was observed in hepatic WD without neurological symptoms. (Hepatology 2021;74:1117-1120).

Wilson disease (WD) is associated with recessive variants in ATPase copper transporting beta (*ATP7B*), 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]

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

When patients with neurological WD were compared to those with hepatic WD, significant reductions of regional brain volumes were observed in the putamen and caudate nucleus of the former ($P < 0.05$; Fig. 1; Supporting 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

Received June 16, 2020; accepted December 2, 2020.

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.31681/suppinfo.

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DOI 10.1002/hep.31681

Potential conflict of interest: Nothing to report.

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
Urine copper, µg/24 hours	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).
*n = 7 (range).
†n = 5 (range).
‡n = 2 (range).
§n = 18.
‖n = 11.
¶n = 7.
#Scores are only reported for patients with cirrhosis.
**Symmetric T1 hyperintensity in the globus pallidus and substantia nigra was present in 2 patients.
Abbreviation: MELD, Model for End-Stage Liver Disease.

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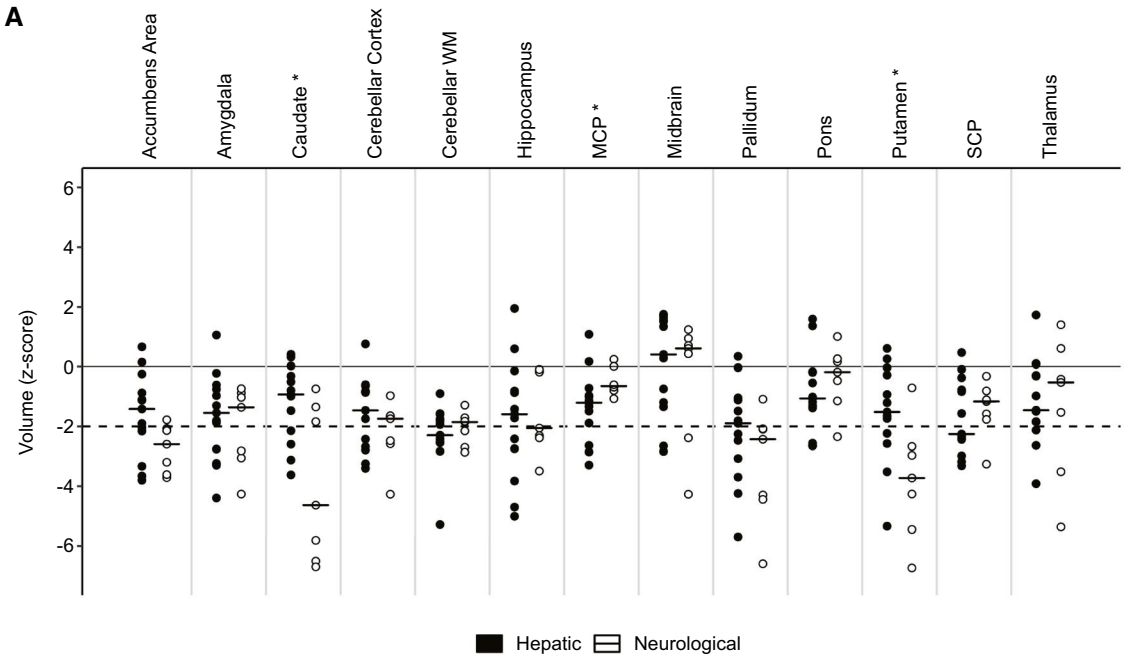
atrophy differed in hepatic and neurological WD, with predominant effects in the cerebellar WM compartment in the former and basal ganglia involvement in the latter. The results indicate that cerebellar atrophy is evident in hepatic WD without neurological symptoms and suggest that the magnitude of striatal atrophy might herald transition from hepatic to neurologic WD.

At present, the pathomechanism responsible for this phenotypical heterogeneity is unknown and



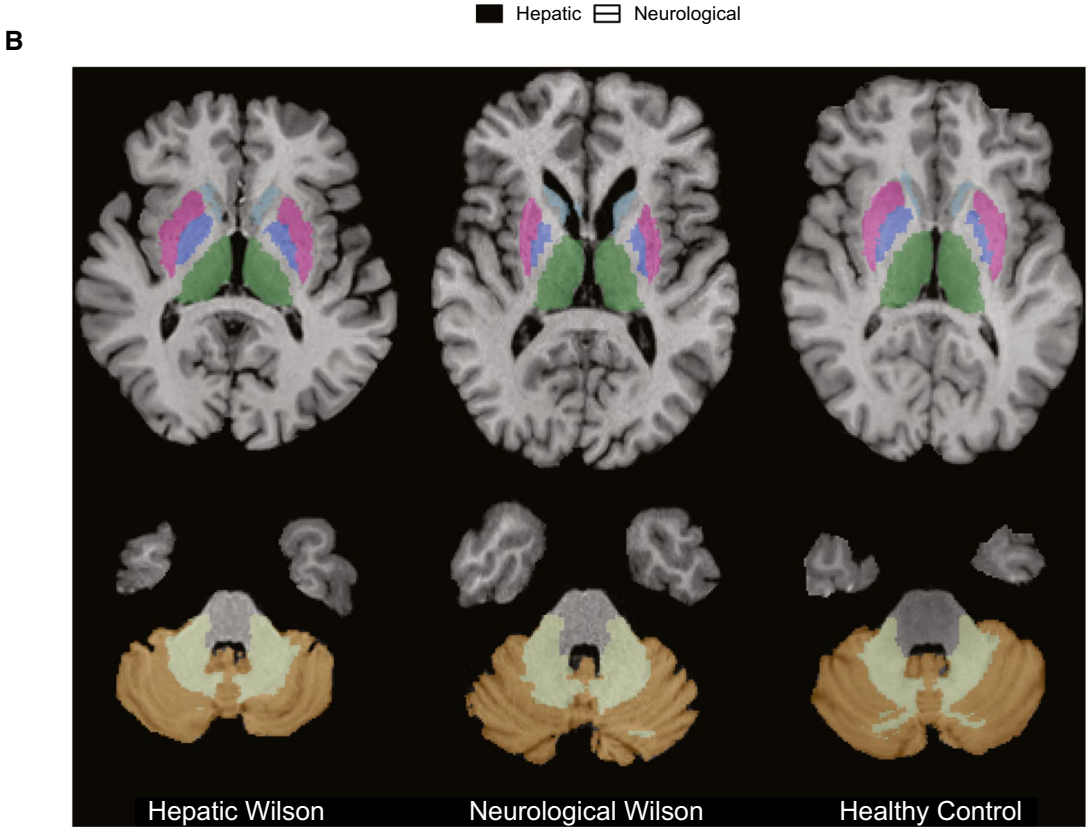


FIG. 1. (A) Subcortical volumetric data expressed as *z* scores for specified subcortical brain regions in patients with hepatic (full circles) or neurologic WD (open circles). Regional medians for each group are marked by horizontal lines. The dashed line at a *z* score of –2.0 serves as a visual reference for severe atrophy. *Statistically significant differences between hepatic and neurological WD. (B) Individual T1-weighted 3-dimensional 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), and cerebellar white matter compartment (yellow). Marked volume reduction can be inferred from smaller colored areas in the cerebellar white compartment and the cerebellar cortex from both patients with WD. In addition, the areas representing the putamen and the caudate of the patient with neurological WD are markedly reduced as an indicator of significant volume reduction in the respective brain regions. The area of the MCP overlaps entirely with the cerebellar white matter compartment as part of it and hence was not separately delineated. Abbreviation: SCP, superior cerebellar peduncle.

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 for a median of 12.5 years after diagnosis, after which pharmacological treatment had been initiated in all but one patient with hepatic WD who underwent liver transplantation shortly after MRI. A potential effect of treatment on subcortical volume can therefore not be excluded. Recent studies have shown qualitative or semiquantitative MRI differences when comparing hepatic and neurologic WD. We objectively quantified volumes of the subcortical brain regions and compared results with age-matched 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 of the appropriate treatment.

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Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.31681/suppinfo.