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 neurological 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.

Normalised 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, significant 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...
## 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 (6.7-16.4)*     | 12.0 (6.5-23.1)*      | 0.50  |
| MELD score                | 9 (8-11)              | 9 (8-11)            | 9 (8-11)              | 1.0   |
| UWDRS score               | 0 (0-33)              | 0 (0-0)             | 27 (10-33)            | <0.001|
| Treatment, n (%)          |                       |                     |                       | 0.52  |
| α-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.

### ARTICLE INFORMATION:

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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 neurological 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 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.