compensated and 36% decompensated). At end of FU, liver disease severity was improved, stable or deteriorated in 20%, 46% and 24% of all cases, respectively. Twenty-eight patients received a liver transplant. Five patients died due to complications of their liver disease and two deaths were related to liver transplantation. In patients who were treated for at least one year (n=111), zinc, penicillamine or trientine (alone, sequentially or combined) were prescribed in 92%, 69% and 14% of patients, respectively. At the end of FU, efficacy of decoppering, based on values of serum non-ceruloplasmin-bound copper concentration (aim: <10 μg/dL) and 24-hour-urinary copper excretion (aim: <100 μg/24 hours), was excellent in 34% of patients, moderate in 42%, poor in 13% and unknown in 11%. Two patients developed HCC. The first patient was a 39-year-old male and presented with decompensated cirrhosis in combination with HCC. The second patient was a 63-year-old female with unequivocal WD diagnosed 50 years earlier. Despite excellent decoppering at the end of FU, she progressed to decompensated cirrhosis in which an HCC developed. No additional risk factors for liver disease were present in both patients. Estimated annual HCC risk for all patients was 0.09% (95% confidence interval: 0.01-0.28). Subgroup analysis in cirrhotic patients revealed an annual HCC risk of 0.14% (95% confidence interval: 0.02-0.45). Conclusion: Even in case of cirrhosis, HCC risk is low in Wilson's disease and appears not related to efficiency of decoppering. Our data do not support regular HCC surveillance in WD.

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Patients with Wilson disease without detectable ATP7B mutations

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Background/aim: Wilson disease (WD) is an inherited autosomal-recessive disorder of hepatic copper excretion resulting in copper accumulation in the liver. The responsible gene mutation is located within the ATP7B gene encoding for a P-type copper transporting ATPase. More than 500 mutations in the ATP7B gene have been described so far. Nevertheless, in up to seven percent of patients with WD, no mutation can be found. Aim of our study was to identify diagnostic characteristics of patients with WD without detectable mutations in ATP7B. Methods: Clinical data and DNA for genetic analysis were obtained from WD patients as part of an international cooperation project. The diagnosis of WD was established if the WD diagnostic score recommended by the EASL Clinical Practice Guidelines on WD was ≥ 4. Mutation analysis was carried out by direct sequencing on an ABI Prism 310 Genetic Analyzer (Perkin Elmer, Norwalk, USA). Next-generation sequencing is ongoing and was performed in ten patients so far. Results: Out of 1294 WD patients collected since 1985 in 65 (5.0%) patients no mutation in the ATP7B gene could be detected. Thirty-nine (60.0%) of them were male. Thirty-one patients (47.7%) presented with neurologic symptoms and 29 (44.6%) with hepatic symptoms (of whom one had fulminant hepatic failure). Five (7.7%) patients were asymptomatic siblings of patients with WD. Mean age at onset of WD was 19.5±10.9 years and 21.4±10.5 years at diagnosis. Kayser-Fleischer corneal rings were present in 38 (58.5%) patients. Hepatic copper content was available in 33 patients (784±586 μg/g dry weight; SD) and coeruloplasmin was decreased in 50 (76.9%) patients (mean: 8.9±7.6 mg/dL). Conclusions: Our data suggest that yet unidentified mutations of genes other than ATP7B might lead to a disease identical to WD. Further research is needed to get more insights into the causes of copper overload in patients without mutations in ATP7B.

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Sex differences in liver SAM:SAH ratios and gene transcript levels after pre-and post-natal choline supplementation and copper chelation treatment in an animal model of Wilson disease

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Background. Methionine metabolism, central to DNA methylation reactions, may provide epigenetic regulation of genes involved in liver damage in Wilson disease (WD). We hypothesized that peri-natal maternal treatment with choline could modify the sex specific response to penicillamine in offspring in the tx-j model of WD. Methods. Control (choline 8 mmol/Kg) or choline supplemented (36 mmol/Kg) diets were fed to wildtype and tx-j female mice starting at 2 weeks before mating and continuing in offspring up to 24 weeks of age. A subgroup of tx-j of both sexes received oral penicillamine with or without choline supplemented diet from 12 to 24 weeks of age. Results. Decreased S-adenosylmethionine (SAM) to S-adenosylhomocysteine (SAH) ratio, an index of DNA methylation capacity, was decreased in each sex of offspring tx-j mice, compatible with the known down-regulation of SAH hydrolase levels in this mouse model of WD (Table 1). The SAM:SAH ratio was higher in untreated female versus male tx-j mice ($p<0.05$). Separate choline or penicillamine treatments were associated with similar increases of SAM:SAH ratio in male tx-j vs wildtype levels. Whereas the ratio was increased by each separate treatment in tx-j males, it was reduced by each separate treatment in tx-j females, but was unchanged in either sex by the combination of choline and penicillamine. Transcript levels of Dnmt3b, a regulator of DNA methylation in tx-j mice, were increased in untreated tx-j of either sex, and were down-regulated by separate or combined penicillamine and choline treatment in male tx-j, but were unchanged by any treatment in female tx-j mice. Grp78 transcript levels were increased in tx-j mice of