EXTRAHEPATIC MANIFESTATIONS OF WILSON DISEASE

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Wilson disease (WD) is a relatively rare inherited disease of copper metabolism. Although it has been recognized and described for nearly a century, our knowledge and understanding of the disease is far from complete. Many patients remain undiagnosed, and diagnosed patients` various symptoms and dysfunctions are often neglected. The aim of this study was to investigate some extrahepatic manifestations, such as skeletal involvement and its mechanism, peripheral sensory and autonomic neuronal changes, and its impact on cardiovascular morbidity. We also determined the temperament and character profile of Wilson patients, and investigated the prevalence of various psychiatric disturbances, among them suicide. Furthermore, we measured the serum level of the newly discovered molecule called nociceptin, and investigated its clinical significance.

Osteopathia has been reported in Wilson disease, but bone density has not been measured; therefore, we performed bone mineral density (BMD), bone mineral content (BMC) and quantitative bone ultrasound (QUS) assessments, as well as measured the serum levels of osteocalcin, (OCN), β-crosslaps (β-CTx) and the recently discovered osteoprotegerin (OPG) and its ligand, RANKL to investigate the underlying mechanism of osseous disorders. Serum OCN, β-CTx, OPG and RANKL levels were measured by ELISA in 21 WD patients and in 20 age and
gender matched healthy subjects. Bone mineral density, and bone mineral content and QUS parameters were also determined. Osteoporosis was present in 9/21 (43%) WD patients. While serum OCN level was similar in patients and controls (29.93±24.65 versus 29.84±6.89 mg/mL), ß-CTx and OPG levels were significantly increased in WD compared to the healthy controls (625.4±312.3pg/mL versus 423.6±144.3pg/mL, p=0.022 and 7.2±3.4pmol/L versus 3.5±1.0pmol/L, p<0.001, respectively). No difference was observed in the RANKL level. There was a positive correlation between OCN and ß-CTx (r:0.55, p=0.01). We proved high occurrence of osteoporosis in Wilson disease. Negative bone remodeling balance is a consequence of increased bone resorption, which is indicated by elevated ß-CTx. The novel finding of elevated serum OPG may reflect a compensatory reaction to enhanced osteoclast activity, despite the normal OCN level.

Autonomic neuropathy, reduced heart rate variability (HRV), which is associated with increased risk for cardiovascular diseases, and peripheral sensory nerve damage have been described in various chronic liver diseases. Wilson disease is characterized by toxic copper accumulation not only in the liver, but also in the brain. Our aim was to assess autonomic and peripheral sensory nerve function in Wilson patients. Twenty two patients with Wilson disease (mean age:32.4±11.8; range:15-52) and 15 age and
gender matched healthy individuals were involved in the study. Peripheral sensory nerve function was assessed on both lower and upper extremities, standard cardiovascular reflex tests and HRV measurements were also performed. Current perception threshold (CPT) was significantly increased for the peroneal nerve in WD (p=0.002). The heart rate variations after standing up and the blood pressure response to sustained handgrip (p<0.05), as well as the time and frequency domain parameters of HRV were significantly reduced in patients with neurological symptoms compared to those without. However, one patient had prominent damage of the median nerve, and 2 patients presented with abnormal cardiovascular reflex tests. One frequency domain parameter correlated with the diastolic ABPM parameters in Wilson patients. This is the first systematic study in WD patients on peripheral sensory neuropathy and autonomic neuropathy based on a sensitive 24-hour heart rate variability analysis. Sensory neuropathy may be the result of direct toxic effect of copper or consequence of liver damage. Altered autonomic function may be caused by copper deposition in the autonomic regulatory centers in the brain.

The initial presentation of Wilson disease may be limited to a wide range of psychiatric disorders without any other symptoms. These patients are often misdiagnosed and mistreated for years. On the other hand, correctly diagnosed Wilson patients’ emotional
distress and other psychiatric conditions are often neglected. Our goal was to investigate the temperament and character changes, as well as the psychiatric manifestations of WD. Thirty Wilson patients and 30 controls completed the Temperament and Character Inventory (TCI) and the Symptom Check List (SCL-90-R) questionnaires. Wilson disease patients significantly deviated from the control group in 2 main temperament and all 3 main character dimensions. In the SCL-90-R 16 out of 30 patients had increased distress and psychological dysfunction. In WD increased scores were present in eight out of the 9 symptoms compared to the controls (p<0.001 for each symptom). Three patients out of 30 attempted suicide. Although the debilitating and life-threatening symptoms are mostly hepatic and neurological, adequate attention should be paid to the psychiatric presentation, because suicide is a relatively common occurrence in WD. Moreover, careful psychiatric exploration should be done because more than half of the patients had increased psychiatric distress, for which psychometric testing seems to be a good screening method.

Plasma level of nociceptin, the endogenous agonist of orphanin FQ/ORL1 receptor was found to be significantly elevated in Wilson disease patients (13.98 ? 2.44 pg/ml, p< 0.001, n =20) compared to age-matched healthy controls (9.18 ? 1.63 pg/ml, n=25). Measurements were performed by $^{125}$I-radioimmunoassay.
Neither sex differences nor correlation between plasma nociceptin levels and liver function test results were found. It is suggested that elevated plasma nociceptin level found in Wilson disease patients is due to inhibition of nociceptin-inactivating zinc-metallopeptidases (aminopeptidase N and endopeptidase 24.15) by the toxic copper deposits in liver and/or brain.

In summary, we found that osteoporosis is very common in young WD patients, most likely secondary to increased osteoclast activity. We also found early dysfunction of peripheral sensory neurons compared to the control group, and decreased heart rate variability only in patients with neurological symptoms, who therefore have increased risk for cardiovascular morbidity. The temperament and character profile deviated from healthy individuals on many scales, and psychiatric symptoms were very common in Wilson patients. We also found a 10% prevalence of attempted suicide among the patients. Nociceptin level was also significantly elevated.

In this study we pinpoint various unsolved questions about the disease, to which we attempted to provide some answers. However, the mysteries about this disease has not all been solved, rather, further questions are raised. I strongly believe, that there are many more interesting and exciting aspects and mechanisms related to the disease, waiting to be explored.