Evolution of exchangeable copper and relative exchangeable copper through the course of Wilson's disease in the Long Evans Cinnamon rat

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Schmitt, Françoise [1], Podevin, Guillaume [2], Poupon, Joël [3], Roux, Jerôme [4], Legras, Pierre [5], Trocello, Jean-Marc [6], Woimant, France [7], Laprévote, Olivier [8], Nguyen, Tuan Huy [9], El Balkhi, Souleiman [10]

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BACKGROUND:
Wilson's disease (WD) is an inherited disorder of copper metabolism leading to liver failure and/or neurological impairment. Its diagnosis often remains difficult even with genetic testing. Relative exchangeable copper (REC) has recently been described as a reliable serum diagnostic marker for WD.

METHODOLOGY/PRINCIPAL FINDINGS:
The aim of this study was to validate the use of REC in the Long Evans Cinnamon (LEC) rat, an animal model for WD, and to study its relevance under different conditions in comparison with conventional markers. Two groups of LEC rats and one group of Long-Evans (LE) rats were clinically and biologically monitored from 6 to 28 weeks of age. One group of LEC rats was given copper-free food. The other groups had normal food. Blood samples were collected each month and different serum markers for WD (namely ceruloplasmin oxidase activity, exchangeable copper (CuEXC), total serum copper and REC) and acute liver failure (serum transaminases and bilirubinemia) were tested. Every LEC rat under normal food developed acute liver failure (ALF), with 40% global mortality. Serum transaminases and bilirubinemia along with total serum copper and exchangeable copper levels increased with the onset of acute liver failure. A correlation was observed between CuEXC values and the severity of ALF. Cut-off values were different between young and adult rats and evolved because of age and/or liver failure. Only REC, with values >19%, was able to discriminate LEC groups from the LE control group at every time point in the study. REC sensitivity and specificity reached 100% in adults rats.

CONCLUSIONS/SIGNIFICANCE:
REC appears to be independent of demographic or clinical data in LEC rats. It is a very simple and reliable blood test for the diagnosis of copper toxicosis owing to a lack of ATP7B function. CuEXC can be used as an accurate biomarker of copper overload.

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