Muscle stiffness, gait instability, and liver cirrhosis in Wilson's disease

Cornelius Kronlage, Martin Hardmeier, Seraina Bally, Marleen Carina Scholz, Heiner C Bucher, Olivia Katharina Müller, Clemens Winterhalder, Michel Mongiat, Jannis Müller, Alexandros Polymeris, Martin Weber, Christina Lausberg, Elianne Kassi, Jens Kuhle, Ludwig Kappos, Wieland Hermann, Christine Bernsmeier, Özgür Yaldizli

Lancet 2020; 396: 990

Neurologic Clinic and Policlinic, (C Kronlage MD, M Hardmeier MD, J Müller MD, A Polymeris MD, J Kuhle MD, Prof L Kappos MD, Ö Yaldizli MD)**, and Division of Internal Medicine** (S Bally MD, M C Scholz MD, O K Müller MD, C Winterhalder MD, M Mongiat MD, M Weber MD, C Lausberg MD, E Kassi MD)**, Department of Medicine, University Hospital Basel, Basel, Switzerland; Basel Institute for Clinical Epidemiology & Biostatistics, Division of Infectious Diseases & Hospital Hygiene, University Hospital Basel, Basel, Switzerland** (Prof H C Bucher MD)**; Department of Neurology, Spital Region Oberaargau, Langenthal, Switzerland** (Prof W Hermann MD)**; and University Centre for Gastrointestinal and Liver Diseases, Basel, Switzerland** (C Bernsmeier MD)

Correspondence to: PD Dr Özgür Yaldizli, Neurologic Clinic and Policlinic, Department of Medicine, University Hospital Basel and University of Basel, Basel 4031, Switzerland
oezguer.yaldizli@usb.ch

See Online for appendix

See Online for video

A 44-year-old night porter presented to our clinic with difficulty walking, instability, and stiffness—particularly in the muscles of his face—which had developed over the previous 3 weeks. His wife said that he had also been tired and lethargic for about 1 year.

He had been seen in our hepatology outpatient clinic 12 months earlier because of a raised aspartate aminotransaminase (AST) of 43 IU/L (normal 11–34) and gamma-glutamyltransferase (GGT) of 301 IU/L (normal 12–68); his alanine aminotransferase (ALT) and bilirubin were normal. Investigations showed no evidence of active viral hepatitis, haemochromatosis, α1 antitrypsin deficiency, or autoimmune liver disease. Serum ceruloplasmin concentration was reduced at 0·11 g/L (normal 0·2–0·6). Ultrasound and transient elastography showed signs of fibrosis and a liver biopsy specimen showed microvesicular steatosis, bilirubinostasis, and severe fibrosis with incomplete cirrhosis. Rhodanine staining for copper was negative. The patient's mother had been diagnosed with Parkinson's disease at age 70 years (see appendix for full family tree).

On examination we found him to have symmetrical cog-wheel muscle rigidity and hypokinetic movements bilaterally. He had diminished arm swing, he was unstable, and when he walked he episodically had short, accelerating steps. He had a mask-like facial expression with a fixed smile—risus sardonicus (figure; video). Investigations found an AST of 128 IU/L, ALT of 131 IU/L, GGT of 497 IU/L, and bilirubin of 64·4 µmol/L (normal <24).

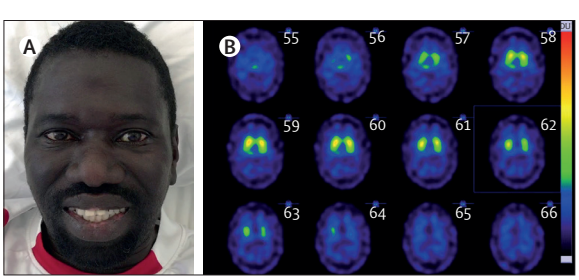

Figure: **Muscle stiffness, instability, and liver cirrhosis**
(A) Mask-like facial expression with a fixed smile—risus sardonicus. (B) A single photon emission CT DaTSCAN (GE Healthcare, Amersham, UK) shows bilaterally reduced presynaptic dopamine transporter in the striatum.

The patient's symptoms deteriorated significantly over the following weeks: he was barely able to walk, he was bradykinetic with episodes of freezing, and he was very unstable on his feet (video). A single photon emission CT DaTSCAN (GE Healthcare, Amersham, UK), 5 weeks after his symptoms began, showed bilaterally reduced presynaptic dopamine transporter in the striatum (figure). Slit-lamp examination of his eyes was normal. The patient's serum ceruloplasmin concentration was again low 0·13 g/L and his urine copper excretion was markedly increased at 5·81 µmol per 24 h (normal <0·95). Histological examination of a biopsy specimen of his liver showed severe progressive chronic hepatitis with cholestasis and fibrosis with complete cirrhosis. Rhodanine staining for copper was again negative. However, analysis using atomic absorption spectrometry showed increased hepatic copper concentrations of 325 µg/g (normal 10–35). We confirmed a diagnosis of Wilson's disease by DNA sequencing, which showed that the patient was homozygous for a missense variant of the *ATP7B*, gene 2998G →A leading to Gly1000Arg substitution.

We started chelation therapy—8 weeks after his neurological symptoms began—with penicillamine. However, the patient's extrapyramidal motor symptoms worsened—probably because of mobilisation of the excess copper and deposition into the basal ganglia. So we switched penicillamine to trientine. The patient's symptoms—apart from the risus sardonicus—showed considerable improvement after 5 months of treatment.

Wilson's disease is an important and treatable differential diagnosis of rapidly developing extra-pyramidal or atypical Parkinsonian symptoms. Even if the patient is over 40 years of age, there are no eye signs—eg Kayser-Fleischer rings, or sunflower cataracts, and conventional histopathological analysis of a liver biopsy with rhodanine stain was negative.

Contributors
We all contributed equally to the diagnosis, care, management, and treatment of the patient. We were all involved in writing the manuscript. Written consent for publication was obtained from the patient.