Letter to the Editor

Unexpected combination of inherited chorea-acanthocytosis with MDR3 (ABCB4) defect mimicking Wilson’s disease

To the Editor:

A 35-year-old Turkish man (III3) born from a consanguineous marriage had been operated on for a bilateral keratoconus while suffering, since the age of 17, from a chronic liver disease of unknown origin. The family history presented the unexplained occurrence of cirrhosis leading to liver transplantation in one cousin (III10) and in one sister (III4) (Fig. 1). Another sister (III2) had developed at the age of 9 a severe picture of genetically demonstrated chorea-acanthocytosis (ChAc) and had died of defenestration 30 years later (Fig. 1). The proband had mild ascite, jaundice and was displaying upper limbs mild choreic movements. Ultrasonography revealed gallbladder lithiasis and splenomegaly. Elevated serum levels of alanine aminotransferase (ALT) and γ-glutamyltransferase (γ-GT) were found to be 10 times the upper normal range and total bilirubin was 391 μmol/l (normal range 6–17 μmol/l), Platelet count had been reduced to 110,000/mm³ and factor V to 49%. Serum ceruleoplasmin level and serum copper concentration were normal, whereas the urinary copper concentration had increased to 1.97 μmol/24 h (normal range from 0.2 to 1 μmol/24 h). A liver biopsy demonstrated micronodular cirrhosis while hepatic copper concentration had increased to 718 μg Cu/g dry liver (normal 5–150). Kayser–Fleischer ring could not be investigated because of the bilateral keratoconus surgery. Wilson’s disease (WD) was evoked and a treatment with zinc sulphate had begun, although a study of the ATP7B gene did not reveal any mutations. Subsequently, the patient presented a first tonic–clonic generalized epileptic seizure followed by a brief episode of delirium. He displayed mild choreic movements of the trunk while all four limb reflexes were absent. Cerebral magnetic resonance imaging (MRI) was normal. Electroneuromyography revealed a sensitive axonal polyneuropathy. Creatine kinase (CK) had increased from 500 to 3000 U/l (normal <50). Acanthocytes were confirmed as absent in the blood after repeated investigations. The direct sequencing of the entire VPS13A gene revealed in patients III2 and III3 the homozygous mutation 4354T>C in exon 37 leading to the missense mutation S1452P and establishing a diagnosis of ChAc (1). The proband status remained stable until the age of 43 when choreic movements of the mouth, the tongue and lip biting appeared. The liver function worsened and transplantation was performed in 2004 leading to a diagnosis of multidrug resistance (MDR3) deficiency (2). Sequencing of the MDR3 [also named adenosine triphosphate-binding cassette, subfamily B, member 4 (ABCB4)] gene on chromosome 7 revealed heterozygous composite missense mutations involving exons 9 (991 C→T) and 23 (2890 C→A) in patients III3 and III4. The proband is now 46 years old and has been seizure free for 7 years, excepting a recent epileptic attack with postictal psychosis and acanthocytosis. He has tongue and lip biting and mild frontal lobe dysfunction, yet no psychosis. The current treatment comprises phenobarbital, tetrabenazine, ursodeoxycholic acid and tacrolimus.

In view of neuropsychiatric signs in a young adult with a liver disorder, including increased urinary copper level and elevated hepatic copper

Fig. 1. Family pedigree. Black corresponds to chorea-acanthocytosis (with homozygous mutations of ChAc) and gray to MDR3/ABCB4 gene defect (with heterozygous composite mutations of the MDR3 gene). The proband (arrow) was affected with both diseases.
concentration, WD became the primary consideration (3). However, despite the lack of acanthocytosis, a genetic based diagnosis of ChAc could be made only subsequently. ChAc occurs in most cases between 25 and 45 years and is characterized by recessively inherited chorea and tics, dystonia or parkinsonism associated with epileptic seizures and axonal polyneuropathy (4). Elevated levels of plasma creatine kinase (CPK), ALT and the presence of acanthocytosis, whose investigation should be repeated, are frequently observed. Blood acanthocytes measurements are frequently performed in neurological practice especially in patients presenting with chorea and may be useful for the diagnosis of neuroacanthocytosis. However, the lack of acanthocytosis must not rule out a diagnosis of ChAc. Hepatic disturbances have never been described in ChAc and were in this patient related to another recessive affection: a defect of the phospholipid export pump coded by the MDR3/ABCB4 gene, encoding the phosphatidyl translocator involved in biliary phosphatidylcholine excretion, responsible for impaired biliary excretion of phosphatidylcholine leading to type 3 progressive familial intrahepatic cholestasis (PFIC3) with elevated -γ-GT level in neonates or children and also the cause of biliary cirrhosis and/or cholelithiasis in young adults (2, 5). The presence of copper deposits is not usually mentioned in MDR3 defects but may be the consequence of cholestatic episodes.

Some signs encountered in our patient should have been helpful to distinguish ChAc from WD and not to start the treatment with zinc sulphate: the ceruleoplasmin serum level is within the normal range in only 5% of WD patients, and chorea, self injurious behavior, peripheral neuropathy as well as normal brain MRI are not suggestive of WD. Moreover, the pathological abnormalities of the liver tissue are different in WD and MDR3 deficiency. In our case, copper deposits were localized in the peripheral hepatocytes of certain nodules corresponding to a cholestatic, non-WD pattern.

This case emphasized that in patients issuing from consanguineous marriages, the combination of two recessively inherited disorders, ChAc and MDR3 deficiency, may mimic WD. The proband’s slowly progressive ChAc phenotype justified the liver transplantation despite the lack of a curative treatment for this disorder.

Acknowledgements
Dr Mathieu Anheim had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. We thank Professor Irmin Sternlieb for both his kind assistance and study of the distribution pattern of hepatic copper deposits.

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