Cameron A. Ackerley,
PhD

Mary Anne Cooper, MD

David G. Munoz, MD

Berge A. Minassian, MD

FATAL HEPATIC FAILURE AND PONTINE AND EXTRAPONTINE MYELINOLYSIS IN XMEA

X-linked myopathy with excessive autophagy (XMEA) is a childhood-onset, slowly progressive myopathy leading to lost ambulation after age 50 years.¹ It is caused by mutations of the *VMA21* gene, which encodes the assembly chaperone of the V-ATPase proton pump that acidifies organelles. Autophagosomal alkalization impairs autophagy completion, which drives autophagosome proliferation and apparent damage to skeletal muscle.² All known XMEA mutations reduce but do not eliminate *VMA21* expression. Some cause greater *VMA21* reduction than in classic XMEA and lead to a severe course with congenital/neonatal onset, extreme muscle wasting, and ventilation dependence. However, even with these mutations, no overt extramuscular disease is present.^{2–5} Given the vital role of V-ATPases in all cells, absence of manifest disease outside muscle is surprising. Possibly, extramuscular pathology is actually present but subclinical. In fact, patients with congenital/neonatal onset do have increased liver function tests, suggesting latent hepatopathy.

We report rapid fatal hepatic cirrhosis at age 52 in one of our cases with otherwise classic XMEA (patient XMEA-12 in reference 2). Brain autopsy revealed surprising extensive myelinolysis. The patient had been a well child until skeletal muscle weakness became evident at age 18, when he could no longer play sports and had difficulty climbing stairs. By age 50, he had difficulty standing, with diffuse muscle wasting most severely in the proximal muscles of the lower limbs, and was no longer able to do his jeweler's work. Routine blood work revealed raised liver function tests; AST was the highest at 3-fold upper limit of normal. He was somewhat overweight (body mass index 28%; upper limit of normal 25%), nondiabetic, did not drink, tested negative for viral and autoimmune hepatitis, and had normal ferritin levels. Progressive worsening of liver function led to liver biopsy, which revealed cirrhosis, but with unique features detailed below. While completing pretransplantation evaluation, stable and well at home, he suddenly decompensated and was hospitalized in intensive care with severe ascites, anasarca, and ventilatory failure. He could not be extubated, became encephalopathic, and subsequently died of esophageal variceal bleeding

10 weeks after admission and 2 years from initial elevated liver enzymes detection.

The biopsied liver was indurated, its external surface “hub-nailed,” and the cut surface nodular. Nodules varied in size, color, shape, and consistency, and fibrous tissue surrounded regenerating nodules, characteristic of macronodular cirrhosis. Steatosis was minimal and there was no frank necrosis. Approximately 75% of hepatocytes in 50% of the nodules were vacuolated, the vacuoles often containing granules (figure 1, A–C), which, with von Kossa staining and energy-dispersive x-ray microanalysis, revealed high calcium content (figure e-1 at Neurology.org), features not seen in common cirrhosis, but typical of the skeletal muscle vacuolar pathology in XMEA.^{3,6} Perls stain for iron was negative.

Brain autopsy revealed no vacuolation of neurons or other cells. Instead, striking well-demarcated areas of demyelination were observed, associated with dense macrophage and reactive astrocyte infiltration and no inflammatory cell infiltrates. The demyelination was in the basis pontis sparing the central area, mammillary bodies, lateral geniculate, putamen, claustrum, and the junction of stratum radiatum and stratum lacunosum moleculare of the anterior hippocampus CA2 sector (figure 1, D–H). Review of intensive care unit records revealed that no significant osmotic shifts had occurred.

VMA21 and V-ATPase are ubiquitous and vital to the whole organism, yet their insufficiency causes a disease so far thought to only affect skeletal muscle. Our patient demonstrates that the same characteristic vacuolation of clinically affected skeletal muscle is also present in the liver, and that therefore XMEA pathology is not in fact restricted to skeletal muscle. In LAMP2 deficiency, the main differential diagnosis of XMEA, extramuscular organs (heart, CNS, liver) are vacuolated⁷ and chronically symptomatic (heart and CNS), but to our knowledge, liver failure and CNS myelinolysis are not reported.

While it is possible that our patient's liver failure was due to nonalcoholic steatohepatitis (even though he was never obese and had insignificant steatosis) or to other causes we did not detect, it is plausible that it was precipitated by his *VMA21* insufficiency. Certainly, the suddenness of liver demise from a well state at home to complete failure and death within weeks was highly unexpected.

Supplemental data
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(A) Nodules (asterisks) surrounded by fibrous tissue derived from degenerated parenchyma typical of end-stage cirrhosis. Arrows indicate vessels and ducts in the fibrous tissue. Masson trichrome stain. Bar, 500 μ m. (B) Low-power electron micrograph of several hepatocytes in a nodule. Note the dense electron opaque vacuolar contents (arrows) and lipid droplets (asterisks) in many of the cells. Bar, 10 μ m. (C) Higher power of unstained section of liver. Arrows indicate electron opaque material in both the cytoplasm and a vacuole, which were subjected to x-ray microanalysis that showed high calcium content. Bar, 500 nm. (D) Histologic sections of the basis pontis stained with Luxol fast blue and hematoxylin & eosin. Note the sharply circumscribed area of demyelination (arrow). Similar equally sharply demarcated areas of demyelination were seen in the mammillary and lateral geniculate bodies (not shown). Bar, 2 mm. (E) High-power micrograph of the pontine lesions in D. Note the survival of neurons (arrowhead) and presence of prominent reactive astrocytes (arrow). Bar, 100 μ m. (F) High-power microscopic section of a lesion similar to D in a mammillary body. Note survival of neurons (arrows) and presence of lipid-laden macrophages (arrowheads). Bar, 100 μ m. The difference between F and E suggests that development of the pontine lesions preceded those in other parts of the brain. (G) Section of the anterior hippocampus immunostained with antibody CD68, which in the brain labels microglia. The location of the abnormality at the junction of stratum radiatum and stratum lacunosum moleculare of the CA2 sector is made apparent. Bar, 2 mm. (H) High power of G (junction of strata radiatum and lacunosum moleculare) showing gemistocytic reactive astrocytes (arrows) and microglia (arrowhead). Bar, 100 μ m. Note that this and other regions of the brain exhibited neuronal survival, and absence of nuclear atypia, rendering, respectively, ischemia and progressive multifocal leukoencephalopathy unlikely alternate causes of the myelinolysis.

Just as the rapid liver collapse was unanticipated, presence of extensive pontine and extrapontine myelinolysis in the brain, unassociated with osmotic shifts, was unexpected. We raise the possibility that the underlying possible CNS V-ATPase deficiency combined with the rapid hepatic failure to subject myelin to acute metabolic challenge.

The patient was one of our oldest XMEA cases. Based on his unexplained acute hepatic and neurologic decompensation, we recommend close clinical, including hepatic, monitoring of patients with this genetic disease, especially as they age.

From the Division of Pathology (C.A.A.), Department of Pathology and Laboratory Medicine, The Hospital for Sick Children, Toronto; Division of Gastroenterology (M.A.C.), Department of Medicine, Sunnybrook Health Sciences Centre and University of Toronto; Division of Pathology (D.G.M.), Department of Laboratory Medicine and Pathobiology, St. Michael's Hospital and University of Toronto; and Division of Neurology (B.A.M.), Department of Paediatrics and Program in Genetics and Genome Biology, The Hospital for Sick Children, and the Institute of Medical Science, University of Toronto, Canada.

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Correspondence to Dr. Minassian: berge.minassian@sickkids.ca

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