Figure Sagittal T2 (fast spin echo), sagittal T2 (fluid-attenuated inversion recovery), and axial T2 (fluid-attenuated inversion recovery) images

Numerous lesions, resembling “cauliflowers,” of heterogeneous intensity on both T2 (fast spin echo) (A, B) and T2 (fluid-attenuated inversion recovery [FLAIR]) (C, D) with a somewhat “bubbly appearance” are protruding from the ventricular walls into the lumen. Multiple high-intensity lesions partly coalescing are demonstrated within the deep and periventricular white matter of the cerebral hemispheres, separated from the ventricular walls by a stripe of normal-appearing white matter (T2 FLAIR) (D). Note the enlarged pretemporal space (a) and the supracerebellar cistern (b) and marked widening of the lateral (c), third (d), and fourth (e) ventricles. The sulci above and below the tentorium are enlarged. The corpus callosum is thin.

chemotherapy-induced peripheral neuropathy indicates a toxic effect on the mitochondria. Prophylactic treatment with ALC has been shown to prevent several drug-induced mitochondrial dysfunctions.⁵ ALC was shown to promote the recovery of nerve conduction velocity.⁴ The imbalance in glutamatergic and GABAergic neurotransmission constitutes one of the mechanisms underlying the CNS degeneration in patients with GA-I.⁶ Recently, glutamate has been described to have a central

role in the transduction of sensory input in the peripheral nervous system.⁷

The possible interaction between carnitine metabolism and the glutamatergic neurotransmission process in the causation of the peripheral neuropathy in GA-I patients remains to be studied.

From the Rambam Health Care Campus (M.H., D.G.), Haifa; Meyer Children’s Hospital (H.M.), Haifa; Sackler School of Medicine (B.-A.S.), Tel-Aviv University; Institute of Chemical Pathology (B.-A.S.), Sheba Medical Center, Tel-Hashomer; and Technion Faculty of Medicine (D.G., H.M.), Haifa, Israel.

Author contributions: Moshe Herskovitz, MD: conceptualization of the study. Dorit Goldsher, MD: conceptualization, analysis and interpretation of data, and revision of the manuscript. Ben-Ami Sela, PhD: analysis and interpretation of data and revision of the manuscript. Hanna Mandel, MD: conceptualization of the study and revision of the manuscript.

Study funding: No targeted funding reported.

Disclosure: The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received December 19, 2012. Accepted in final form April 5, 2013.

Correspondence to Dr. Herskovitz: m_herskovitz@rambam.health.gov.il

© 2013 American Academy of Neurology

1. Harting I, Neumaier-Probst E, Seitz A, et al. Dynamic changes of striatal and extrastriatal abnormalities in glutaric aciduria type I. *Brain* 2009;132:1764–1782.
2. Korman SH, Jakobs C, Darmin PS, et al. Glutaric aciduria type 1: clinical, biochemical and molecular findings in patients from Israel. *Eur J Paediatr Neurol* 2007;11:81–89.
3. Zhang W, Miao J, Zhang G, et al. Muscle carnitine deficiency: adult onset lipid storage myopathy with sensory neuropathy. *Neurol Sci* 2010;31:61–64.
4. Sim KG, Carpenter K, Hammond J, Christodoulou J, Wilcken B. Acylcarnitine profiles in fibroblasts from patients with respiratory chain defects can resemble those from patients with mitochondrial fatty acid beta-oxidation disorders. *Metabolism* 2002;51:366–371.
5. Zheng H, Xiao WH, Bennett GJ. Mitotoxicity and bortezomib-induced chronic painful peripheral neuropathy. *Exp Neurol* 2012;238:225–234.
6. Kölker S, Koeller DM, Okun JG, Hoffmann GF. Pathomechanisms of neurodegeneration in glutaryl-CoA dehydrogenase deficiency. *Ann Neurol* 2004;55:7–12.
7. Tremolizzo L, Sala G, Zoia CP, Ferrarese C. Assessing glutamatergic function and dysfunction in peripheral tissues. *Curr Med Chem* 2012;19:1310–1315.

Naila Makhani, MD,
MPH
Bo-ye Ngan, MD, PhD
Binita M. Kamath,
MBBChir
E. Ann Yeh, MD

GLATIRAMER ACETATE-INDUCED ACUTE HEPATOTOXICITY IN AN ADOLESCENT WITH MS

Glacitamer acetate (GA), a synthetic copolymer, is a frequently used first-line treatment for relapsing-remitting multiple sclerosis (RRMS). Probable autoimmune hepatotoxicity during GA treatment has been reported,^{1–4} but GA hepatotoxicity in the absence of positive autoimmune markers has not previously been described. Here, we report GA-induced hepatotoxicity in a pediatric patient with multiple sclerosis (MS).

Case report. We diagnosed a 15-year-old girl with RRMS following 2 attacks of brainstem signs and symptoms (October and December 2011) with fluid-attenuated inversion recovery signal abnormalities on MRI characteristic for MS and spinal fluid analysis that revealed the presence of oligoclonal bands. We initiated immunomodulatory therapy with subcutaneous (SC) interferon- β -1a in February 2012 and titrated the dose gradually to 44 μ g 3 times a week. Our patient had no other medical conditions

Supplemental data at
www.neurology.org

Figure 1 Liver transaminases over time and liver pathology in a 15-year-old patient with multiple sclerosis

(A) Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels in our patient. Arrows indicate time of initiation of interferon-β-1a (IFN) and glatiramer acetate (GA). Pathology shows (B) isolated single hepatocyte cell death at earliest phase (blue arrow) and (C) late phase hepatocyte death triggering an inflammatory response. (D) Immunostain for CD8+ cytotoxic T cells shows that these are the principal cells of the inflammatory response.

and was taking no other prescribed or herbal medications. There was a remote history of transient unexplained jaundice in her father. Aspartate aminotransferase (AST = 370, normal range 0–36) and alanine aminotransferase (ALT 145, normal range 0–40) were elevated in May 2012 and we discontinued interferon therapy. Liver transaminases normalized by August 2012 (AST 20 and ALT 35) and we initiated GA at a dose of 20 mg SC once daily (figure 1A).

In October 2012, routine blood tests showed elevated ALT (253) and serum ferritin (119, normal range 5.5–67.4). Repeat testing 1 week later revealed further elevations in ALT, AST, and serum ferritin (figure 1A). Physical examination revealed no jaundice, hepatomegaly, or other stigmata of liver disease. Our patient's only symptom was profound fatigue. Hepatic ultrasound showed nonspecific echogenicities suggestive of fatty infiltration without hepatomegaly. Liver function tests including serum international normalized ratio, partial thromboplastin time, bilirubin, and albumin were normal. Total white blood cell count, hemoglobin, and platelet levels were normal. Inflammatory markers including

erythrocyte sedimentation rate and C-reactive protein were normal as was serum iron. Serologic tests for recent Epstein-Barr virus infection and for hepatitis A, B, and C were negative. Tests for autoimmune hepatitis including antinuclear antibody (ANA), anti-smooth muscle antibody, antiliver/kidney antibody, and immunoglobulin G (IgG) levels were all normal.

Liver biopsy revealed a mild parenchymal, mainly CD8+, lymphocytic inflammatory infiltrate within the portal tracts with mild portal fibrosis, no plasma cells, and no signs of chronic liver disease (figure 1, B–D). There was hepatocyte necrosis. Cytomegalovirus and adenovirus immunostains were negative. Electron microscopy revealed microvesicular steatosis and increased intracellular lipofuscin deposition with mild smooth endoplasmic reticulum and mitochondrial proliferation (figure e-1 on the *Neurology*® Web site at www.neurology.org). Some mitochondria showed nonspecific reactive changes, were enlarged, and contained crystalline inclusions. Necrotic cells did not show activation or cytoplasmic expression of the apoptotic pathway protein Caspase-3 by immunohistochemistry, suggesting a nonapoptotic cellular death mechanism. The liver biopsy was

consistent with drug-induced hepatocellular injury with mitochondrial damage.

We discontinued GA therapy on November 7, 2012. Liver transaminases and serum ferritin normalized by December 31, 2012.

Discussion. GA has been linked to the development or exacerbation of autoimmune conditions including myasthenia gravis,⁵ autoimmune hyperthyroidism,⁶ and autoimmune hepatitis.^{1,2} There was no evidence for autoimmune injury in our patient as ANA, anti-smooth muscle, and antiliver/kidney antibodies were absent, serum IgG level was normal, and there was no plasma cell infiltrate on liver histology. Instead the microvesicular steatosis, hepatocyte necrosis, and structural mitochondrial changes suggest cell death mediated by mitochondrial metabolic stress activation, a novel pattern of drug-induced injury associated with GA. This pattern is well-recognized with other drugs and the presumed mechanism is inhibition of mitochondrial function with accumulation of reactive oxygen species, lipid peroxidation with fat accumulation, and cell death.⁷

Although 2 prior case reports described possible GA hepatotoxicity, the patient in the first report had a concomitant elevated ANA titer (1:320),⁴ and the patient in the second report displayed anti-smooth muscle antibodies acutely (1:320),³ suggesting underlying autoimmune mechanisms as opposed to direct toxic injury.

Importantly, our patient previously displayed elevated liver transaminases with interferon- β -1a treatment, resulting in interferon discontinuation and a switch to GA. While interferon-induced hepatotoxicity has successfully been managed by changing to GA,² this case suggests that, for some patients, transaminitis with interferon treatment may signal a predisposition to GA-induced hepatotoxicity.

This report should alert practitioners to the possibility of acute hepatitis induced by GA. While regulatory agencies currently do not require blood tests for safety monitoring during GA treatment, we suggest that individuals who commence GA following transaminitis with interferons should be regularly monitored for signs of hepatotoxicity. Hepatotoxicity occurred within 3 months of therapy initiation, suggesting early

monitoring of transaminases is necessary. Increased vigilance may be warranted in children.

From the Hospital for Sick Children (N.M., B.N., B.M.K., E.A.Y.) and University of Toronto (N.M., B.N., B.M.K., E.A.Y.), Canada.

Author contributions: Dr. Makhani: data acquisition, data analysis, drafting of the manuscript, and review of manuscript for important intellectual content. Dr. Ngan: data acquisition, data analysis, drafting of the manuscript, and review of the manuscript for important intellectual content. Dr. Kamath: data acquisition, data analysis, and review of the manuscript for important intellectual content. Dr. Yeh: data acquisition, data analysis, review of the manuscript for important intellectual content, and study supervision.

Acknowledgement: The authors thank Lynn MacMillan for assistance in acquiring patient data for this report.

Study funding: No targeted funding reported.

Disclosure: N. Makhani received fellowship funding from the Canadian Network of MS Clinics and has received research support from the Dairy Farmers of Ontario. She has received speaker's honoraria from EMD Serono and Teva Neuroscience. B. Ngan reports no disclosures. B. Kamath has received research support from the SickKids Transplant and Regenerative Medicine Center, Allergie Syndrome Alliance, the SickKids Research Institute, NIH, Ashley's Angels Foundation, Rare Disease Foundation, and the American Liver Foundation. E. Yeh has received research support from the National MS Society, MS Society of Canada, CIHR, NIH, the Dairy Farmers of Ontario, Jog for the Jake Foundation, and the Children's Guild Foundation. Go to Neurology.org for full disclosures.

Received February 20, 2013. Accepted in final form May 7, 2013.

Correspondence to Dr. Makhani: Naila.makhani@sickkids.ca

© 2013 American Academy of Neurology

1. Neumann H, Csepregi A, Sailer M, Malfertheiner P. Glatiramer acetate induced acute exacerbation of autoimmune hepatitis in a patient with multiple sclerosis. *J Neurol* 2007;254:816–817.
2. Pulicken M, Koteish A, DeBusk K, Calabresi PA. Unmasking of autoimmune hepatitis in a patient with MS following interferon beta therapy. *Neurology* 2006;66:1954–1955.
3. Subramaniam K, Pavli P, Llewellyn H, Chitturi S. Glatiramer acetate induced hepatotoxicity. *Curr Drug Saf* 2012;7:186–188.
4. Deltenre P, Peny MO, Dufour A, Nady ME, Henrion J. Acute hepatitis induced by glatiramer acetate. *BMJ Case Rep* 2009;2009.
5. Frese A, Bethke F, Ludemann P, Stogbauer F. Development of myasthenia gravis in a patient with multiple sclerosis during treatment with glatiramer acetate. *J Neurol* 2000;247:713.
6. Heesen C, Gbadamosi J, Schoser BG, Pohlau D. Autoimmune hyperthyroidism in multiple sclerosis under treatment with glatiramer acetate: a case report. *Eur J Neurol Official J Eur Fed Neurol Societies* 2001;8:199.
7. Navarro VJ, Senior JR. Drug-related hepatotoxicity. *N Engl J Med* 2006;354:731–739.