

Severe Hypercholesterolemia Mediated by Lipoprotein X in a Pediatric Patient with Chronic Graft-Versus-Host Disease of the Liver



Hanaa Zidan, M.D., Stanley Lo, Ph.D., Donald Wiebe, Ph.D., Julie Talano, M.D., and Ramin Alemzadeh, M.D.

Department of Pediatrics (H.Z., J.T., R.A.) and Department of Pathology (S.L.), Medical College of Wisconsin, Milwaukee, Wisconsin; and Department of Pathology & Laboratory Medicine (D.W.), University of Wisconsin, Madison, Wisconsin

We describe a case of extreme hypercholesterolemia, mediated by lipoprotein X (LpX), in a 12-yr-old Caucasian female who underwent an unrelated allogeneic bone marrow transplant for relapsed acute myelocytic leukemia (AML). Her posttransplant course was complicated by severe chronic graft-*vs.*-host disease (GVHD) of the liver. Previously normal serum cholesterol and triglycerides rose to 1122 mg/dl (29.0 mmol/liter) and 1100 mg/dl (12.4 mmol/liter), respectively. Serum cholesterol appeared to be dominantly carried by LpX. Intrahepatic cholestasis leading to reflux of bile lipoproteins into the blood stream and subsequent formation of LpX appears to be the mechanism underlying this phenomenon. Severe hypercholesterolemia mediated by LpX after BMT has not been reported in the pediatric literature.

Introduction

Hypercholesterolemia is a common disorder in adult population, but extreme levels beyond 1000 mg/dl (25.8 mmol/liter) are only found in patients with homozygous familial hypercholesterolemia (1), hepatic lipase deficiency (2), and obstructive biliary cholestasis (3, 4). Complications include premature coronary artery disease (5), hyperviscosity syndrome (6), retinal cholesterol thromboembolism, and cholesteroloma (7). Treatment options include medica-

tion (dietary cholesterol binding agents and cholesterol synthesis inhibitors statins) (8, 9), aphaeresis (10), and plasmapheresis (6).

One of the known complications of allogeneic BMT is chronic graft-*vs.*-host disease (GVHD), which occurs in up to 21.3% of recipients depending on the induction therapy (11). Chronic GVHD of the liver is characterized by elevation of hepatic enzymes along with a cholestatic picture and extreme elevations of cholesterol and triglycerides (in excess of 1000 mg/dl). To date, there have been five reported cases of liver GVHD-mediated by severe hypercholesterolemia in the adult literature (7, 12, 13), but none has been reported in the pediatric literature.

Case Report

A 12-yr-old female patient with acute myelocytic leukemia (AML) underwent an allogeneic hematopoietic stem cell transplant that subsequently was complicated by chronic GVHD of the liver and gastrointestinal tract, evidenced by liver biopsy, after 14 months posttransplant. Her liver enzymes: aspartate aminotransferase (AST) 291 IU/liter (16–46), alanine aminotransferase (ALT) 644 IU/liter (3–35) and γ -glutamyltransferase (GGT) 1010 IU/liter (15–85), total protein 53 g/liter

(59–77), albumin 30 g/liter (38–54), total bilirubin 84 mg/liter (1–11), direct bilirubin 50 mg/liter (0–30), prothrombin time (PT) 12.4 sec (12.1–14.2), and an international normalization ratio (INR) of 0.89. She was referred to the endocrine service for evaluation and management of elevated total cholesterol of 1122 mg/dl (29.0 mmol/liter) and triglycerides 1100 mg/dl (12.4 mmol/liter). Her serum cholesterol and triglycerides levels before BMT were normal, total cholesterol 127 mg/dl (125–200), and triglycerides 112 mg/dl (39–140). Her plasma lipid levels progressively increased over a period of 1 yr and reached their maximum levels at the time of presentation. Her past medical history was significant for depression. There is no family history of hypercholesterolemia. Her medications included tacrolimus, methylprednisolone (60 mg/d), mycophenolate, pentamidine, amphotericin B, acyclovir, and escitalopram oxalate. Her physical examination was noncontributory except for cushingoid features.

Initial Laboratory Studies

One-milliliter aliquots of both specimens (pre- and postplasmapheresis) were ultracentrifuged in a Beckman Optima using 100.2 titanium rotor at 100,000 rpm ($\sim 350,000 \times g$) for 3 h. Sequential ultracentrifugation of the se-

continued on page 3



LETTER FROM THE PRESIDENT

Spring in the Midwest always brings the promise of growth and a hopeful look towards the future. For EFF, this spring has brought both. We completed our spring grant cycle in April and awarded a record total of 15 grants to young investigators in the areas of diabetes, metabolism, obesity, and general endocrinology. We appreciate the generous support of Amylin and Bristol-Myers in enabling EFF to expand our grant program. The fall cycle will offer a new initiative. The investigators grant program in diabetes, obesity, and metabolism will allow for funding for academicians in their first 2 years beyond fellowship, and there-

fore, we hope to help bridge the transitional gap between training and career for our graduating fellows.

June brings our annual pre-American Diabetes Association forum with an outstanding faculty assembled. Look for the content of this meeting to appear in streaming format online in late summer. Summer also brings endocrine grand rounds, a monthly streaming audio conference on topics in endocrinology. We are also looking to bring online clinical case discussion groups to our web site. Feel free to submit a case and serve as our online moderator. We welcome any suggestions on new initiatives for web-based education.

These are difficult and uncharted economic and regulatory times we face in all aspects of health care and medical education. These challenges have stressed our main source of educational support, the pharmaceutical industry. However, we at EFF remain proud of our efforts to raise awareness of fellow-based educational initiatives, and there is a strong recognition among industry of the importance of our future thought leaders. The Board remains committed to securing support for expanded opportunities for fellows in the coming year. We'll see many of you in New Orleans!

Sincerely,
Mark Stolar, M.D.
President



Severe Hypercholesterolemia Mediated by Lipoprotein X
Page 1



Letter from the President
Page 2



Pituitary Adenoma and GnRH Agonist Therapy
Page 4



Lithium Toxicity and Hyperparathyroidism
Page 6



Nutritional Management of Gestational Diabetes Mellitus
Page 9



Testicular Adrenal Rest Tumors
Page 11



Functioning Metastases in Metastatic Thyroid Carcinoma
Page 12



Foundation News
Page 14



Calendar of Events
Page 16

EndoTrends

A Publication of the Endocrine Fellows Foundation
Dedicated to Diabetology, Endocrinology, and Metabolism

© Copyright 2009 by the Endocrine Fellows Foundation (EFF). All rights reserved. No part of this publication may be reproduced or transmitted by any means without permission from the EFF. Printed by Cadmus Communications, a Cenveo Company. All correspondence related to manuscripts should be sent to the EFF. The views and opinions expressed in *EndoTrends* are solely those of the authors. They are presented as a professional service to the medical community and do not necessarily reflect the views of the publisher.

EFF Office

1310 19th Street NW
Washington, DC 20036
Toll Free: 877-877-6515
Fax: 860-586-7550
www.endocrinefellows.org
E-mail: info@endocrinefellows.org

Editor-in-Chief

Ramachandiran Cooppan, M.D.

Associate Editors

Ariel Barkan, M.D. Robert Rapaport, M.D.
Rogerio Lobo, M.D. Joseph R. Tucci, M.D.

Endocrine Fellows Foundation Staff

Executive Director: Anne Mercer
Cadmus (Cenveo) Staff
Editor: Trisha Gage
Account Manager: Teressa Beard

ADDRESS UPDATE

Please keep the Endocrine Fellows Foundation advised of any address changes by calling, faxing, or e-mailing as shown below:

Toll Free: (877) 877-6515 Fax: (860) 586-7550 E-Mail: info@endocrinefellows.org

Thank you.

EFF Board of Directors

**John P. Bilezikian, MD
Chair**

Professor of Medicine &
Pharmacology

Chief, Division of
Endocrinology; College of
Physicians & Surgeons

Columbia University
New York, NY



**Mark Stolar, MD
President**

Associate Professor of
Clinical Medicine

Northwestern University
Medical School

Chicago, IL



**Ramachandiran
Cooppan, MD**

EndoTrends Editor-in-Chief

Assistant Clinical Professor
of Medicine

Harvard Medical School

Consultant
The Joslin Diabetes Center

Boston, MA



David Kendall, MD

Medical Director and Chief
Clinical and Professional
Services

International Diabetes
Center

Minneapolis, MN



Derek Le Roith, MD, PhD

Chief, Division of Endocrinology,
Diabetes and Bone Diseases

Professor, Molecular Medicine

Department of Medicine

The Mount Sinai School
of Medicine

New York, NY



**Sherman M. Holvey, MD
Past President and Founder**

Clinical Professor of
Medicine, Emeritus

Department of Medicine
University of California
School of Medicine

Los Angeles, CA



continued from page 1

Severe Hypercholesterolemia Mediated by Lipoprotein X in a Pediatric Patient with Chronic Graft-Versus-Host Disease of the Liver

rum specimens at the density of serum (1.006 gm/ml) and at 1.063 gm/ml with the addition of powder potassium bromide separated the very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) from the high-density lipoprotein (HDL) and serum proteins that were left in the lower fraction of the final tube. Cholesterol and GGT were measured in the bottom fractions. The initial specimen gave a bottom fraction with cholesterol of 719 mg/dl (18.6 mmol/liter) and GGT of 3147 U/liter. The analysis of the second fraction (postplasmapheresis) revealed cholesterol and GGT levels of 248 mg/dl (6.4 mmol/liter) and 591 U/liter, respectively. The 1.063-g/ml bottom fractions were analyzed for cholesterol and GGT. The cholesterol in the bottom fraction for the initial sample was found to be 20 mg/dl and represents the patient's HDL-cholesterol value. The second sample after plasmapheresis had a bottom cholesterol value of only 6 mg/dl and suggests that plasmapheresis was successful at reducing the plasma components by approximately 75%. The rationale for separation and measuring the GGT activity in the bottom fractions was to demonstrate the presence of li-

poprotein X (LpX). Typically, all serum GGT should be recovered in the bottom fraction. However, 35–46% of the GGT activity was lost with the top 1.063-g/ml fraction, which suggests that the enzyme is bound to an abnormal lipoprotein particle, in this case, LpX, which is formed when the bile is regurgitated back into circulation.

The patient was started on fish oil, 3 g twice daily (180 mg eicosapentaenoic and 120 mg docosahexanoic acid). Also, she underwent plasmapheresis several times after which her serum cholesterol and triglycerides decreased; however, they returned to high levels before each subsequent procedure.

Discussion

This is the first reported pediatric case of hypercholesterolemia mediated by LpX. Severe hypercholesterolemia is becoming more frequent as allogeneic hematopoietic stem transplant is becoming the standard of care for many diseases, especially in oncology patients. Medications can cause hypercholesterolemia including but not limited to cyclosporine (14, 15), sirolimus (16,

17), mycophenolate (18), and glucocorticoids (19). However, these medications can often result in elevation of total serum cholesterol levels that rarely exceed 300 mg/dl and are usually mediated by LDL cholesterol. In our patient, hypercholesterolemia was the result of the cholestasis and failure of cholesterol and bile salts clearance through the bile duct. Consequently, regurgitation of cholesterol and bile salts into the circulation leads to elevated serum cholesterol level associated with LpX and not due to overproduction by hepatocytes. Thus, the use of statin drugs to down-regulate cholesterol synthesis is not deemed effective. Hypothyroidism in its severe form can cause hyperlipidemia (20), but it was ruled out because the patient had a normal thyroid function.

LpX is present in sera of patients with intra- or extrahepatic cholestasis, lecithin cholesterol acyl transferase (LCAT) deficiency and newborns with immature liver function (18, 21). Previously normal lipid levels in our patient exclude these conditions. Hyperlipidemia secondary to intrahepatic cholestasis

continued on page 4

continued from page 3

caused by chronic GVHD can appear between any time between 2 months and 2 yr after transplantation. Complication in the form of exanthemata, retinal thromboembolism, or cholesteroloma of the lung has been reported in adult patients with severe hypercholesterolemia (12), but none in our patient. Moreover, there was not sufficient time to observe for development of vascular disease. In conclusion, severe hypercholesterolemia mediated by LpX as a complication of chronic liver GVHD after BMT is becoming a recognized phenomenon in pediatric patients. Therefore, medical care providers treating children at risk of developing chronic liver GVHD should identify this condition to initiate intervention early during the course of the illness.

References

1. Sprecher DL, Schaefer EJ, Kent KM, Gregg RE, Zech LA, Hoeg JM, McManus B, Roberts WC and Brewer HB. Cardiovascular features of homozygous familial hypercholesterolemia: analysis of 16 patients. *Am J Cardiol.* 1984; 54:20–30.
2. Connelly PW & Hegele RA. Hepatic lipase deficiency. *Crit Rev Clin Lab Sci.* 1998; 35:547–572.
3. McIntyre N, Harry DS, Pearson AJG. The hypercholesterolaemia of obstructive jaundice. *Gut.* 1975; 16:379–391.
4. Dickson ER, Fleming CR, Ludwig J. Primary biliary cirrhosis. In: Popper H, Schaffner F, eds. *Progress in liver diseases* Vol. 6. New York: Grune & Stratton; 1979; pp 487–528.
5. Coetzee GA, van der Westhuyzen DR, Berger GM, Henderson HE, Gevers W. Low-density lipoprotein metabolism in cultured fibroblasts from a new group of patients presenting clinically with homozygous familial hypercholesterolemia. *Arteriosclerosis.* 1982; 2:303–311.
6. Rosenson RS, Baker AL, Chow MJ, Hay RV. Hyperviscosity syndrome in a hypercholesterolemic patient with primary biliary cirrhosis. *Gastroenterology.* 1990; 98:1351–1357.
7. Toren A, Nagler A. Solitary pulmonary cholesteroloma, multiple xanthelasma, lipemia retinalis complicating hypercholesterolemia after bone marrow transplantation. *Bone Marrow Transplant.* 1996; 18:457–459.
8. Illingworth DR. How effective is drug therapy in heterozygous familial hypercholesterolemia? *Am J Cardiol.* 1993; 72:54D–58D.
9. Malloy MJ, Kane JP, Kunitake ST, Tun P. Complementarity of colestipol, niacin, lovastatin in treatment of severe familial hypercholesterolemia. *Ann Intern Med.* 1987; 107:616–623.
10. Gordon BR, Kelsey SF, Bilheimer DW, Brown DC, Dau PC, Gotto AM, Illingworth DR, Jones PH, Leitman SF, Prihoda JS, Stein EA, Stern TN, Zavoral JH, Ziwiener RJ. Treatment of refractory familial hypercholesterolemia by low-density lipoprotein apheresis using an automated dextran sulfate cellulose adsorption system. The Liposorber Study Group. *Am J Cardiol.* 1992; 70:1010–1016.
11. Neudorf S, Sanders J, Kobrinsky N, Alonzo T A, Buxton AB, Gold S, Barnard DR, Wallace JD, Kalousek D, Lange BJ, Woods WG. Allogeneic bone marrow transplantation for children with acute myelocytic leukemia in first remission demonstrates a role for graft versus leukemia in the maintenance of disease-free survival. *Blood.* 2004; 103:3655–3661.
12. Coakley JC, Vervaart PP, McKay MRG. Factitious hyponatremia in a patient with cholestatic jaundice following bone marrow transplantation. *Pathology.* 1986; 18:158–159.
13. Turrchin A, Wiebe DA, Seely EW, Graham T, Longo W, Soiffer R. Severe hypercholesterolemia mediated by lipoprotein X in patients with chronic graft-versus-host disease of liver. *Bone Marrow Transplant.* 2005; 35:85–89.
14. Kuster GM, Drexel H, Bleisch JA, Rentsch K, Pei P, Binswanger U, Amann FW. Relation of cyclosporine blood levels to adverse effects on lipoproteins. *Transplantation.* 1994; 57:1479–1483.
15. Satterthwaite R, Aswad S, Sunga V, Shidban H, Bogaard T, Asai P, Khetan U, Akra I, Mendez RG, Mendez Robert. Incidence of new-onset hypercholesterolemia in renal transplant patients treated with FK506 or cyclosporine. *Transplantation.* 1998; 65:446–449.
16. Chueh SC, Kahan BD. Dyslipidemia in renal transplant recipients treated with a sirolimus, cyclosporine-based immunosuppressive regimen: incidence, risk factors, progression, and prognosis. *Transplantation.* 2003; 76:375–382.
17. Morrisett JD, Abdel-Fattah G, Hoogeveen R, Mitchell E, Pownall HJ, Opekun AR, Jaffe JS, Oppermann S, Kahan BD. Effects of sirolimus on plasma lipids, lipoprotein levels, fatty acid metabolism in renal transplant patients. *J Lipid Res.* 2002; 43:1170–1180.
18. Roche Laboratories. Cellcept® (mycophenolate mofetil) Complete Product Information (online), 2004 (cited October 14, 2004). Available from <http://www.rochusa.com/products/cellcept/pi.pdf>.
19. Sholter DE, Armstrong PW. Adverse effects of corticosteroids on the cardiovascular system. *Can J Cardiol.* 2000; 16:505–511.
20. O'Brien T, Dinneen SF, O'Brien PC, Palumbo PJ. Hyperlipidemia in patients with primary, secondary hypothyroidism. *Mayo Clin Proc.* 1993; 68:860–866.
21. Glomset JA, Nichols AV, Norum KR, King W, Forte T. Plasma lipoproteins in familial lecithin-cholesterol acyltransferase deficiency. *J Clin Invest.* 1973; 52:1078–1092.



Case Report

Pituitary Adenoma and GnRH Agonist Therapy for Precocious Puberty

Rishita Tiwari, M.D., Holley Allen, M.D., and Edward Reiter, M.D.

Department of Pediatric Endocrinology, Baystate Medical Center, Tufts University School of Medicine, Springfield, Massachusetts

Case Report

B.C. is a 10-yr-old female referred for continued treatment of precocious puberty. She transferred care from out of state to our clinic. She was diagnosed with central precocious puberty in November 2003 at age 6 yr and was started on monthly leuprolide acetate depot injections (dose unknown), which was increased to 11.25 mg after 1 yr of treatment. She was maintained at 11.25 mg until her

move to Massachusetts. According to mother, B.C.'s breast development as well as pubic hair seemed to progress but she remained pre-menarchal.

B.C. also had ADHD, severe depression, self-inflicting abuse, post-traumatic stress disorder, and behavioral issues. B.C. was obese and has a history of hiding and stealing food. Her development was normal until age 2 yr, coinciding with her father's death. Mother reports that B.C. stopped speaking abruptly soon af-

ter her father's death and remained silent for 2 yr. B.C. has required speech therapy since that time. Her other medications include Focalin 10 mg once daily. She was a normal full-term baby without neonatal complications. The mother's pregnancy was uneventful.

Her review of systems was positive for frequent frontal headaches unaccompanied by nausea, vomiting, or visual dis-

continued on page 5

continued from page 4

turbances. Headaches were described as mild and relieved with ibuprofen. There was no history of seizures or diplopia. She had mild acne, occasional constipation, and nocturnal enuresis. The family history was significant for autism and Asperger syndrome in a niece and nephew, respectively. There was no family history of precocious puberty. Mother's menarche was at age 12 yr.

On examination her pulse rate, respiratory rate, and blood pressure were normal. Her weight was 207 lbs with a height of 5 ft, 4 in., which is above 97th percentile for weight as well as height. Her BMI was at 99.7th percentile for age. She had coarse features. Her skin was thick and dry. There were several hypopigmented striae on breasts and abdomen. There was acanthosis on her neck, axillae, and groin area. She had an abnormal fat distribution, including a buffalo hump, but no moon facies. The neurological exam was unremarkable. She had normal muscle tone and reflexes. Her vision was normal. Her hands and feet were proportional to her body. Her breast sexual maturity rating was 5. There was no expressible discharge from the nipples. Pubic hair sexual maturity rating was 4. She had adult-type axillary hair distribution.

We did not receive any record of imaging studies from her previous endocrinologist. We were concerned about the history of headaches and her progressive pubertal and height development. We obtained a magnetic resonance imaging (MRI) of her brain, which showed a pituitary adenoma of size 10 × 8 × 11 mm. The report specifically mentioned that the anterior lobe was prominent and it was triangular in shape. The neurosurgeon felt that the image on MRI could be pituitary hypertrophy and not a tumor and hence did not require surgical removal. We tested other hormones to evaluate for secretory tumors of the pituitary gland. See Table 1. She had normal levels of IGF-I, random GH, prolactin, ACTH, and α -subunit as well as prepubertal FSH, LH, and estradiol levels. B.C. was receiving monthly leuprolide acetate depot injections at the time. Her thyroid function tests were in the normal range. We also evaluated

Table 1
Evaluation Results

Test	Level
FSH (0.3–11.1)	1.1 mIU/ml
LH (0.0–3.10)	0.1 mIU/ml
Estradiol (0–70)	<3 pg/ml
IGF-I (88–452)	326 ng/ml
ACTH (6–48)	33 pg/ml
TSH (0.4–4.0)	2.76 mIU/ml
Free T ₄ (0.7–1.8)	0.97 ng/dl
GH (0–5)	0.11 ng/ml
Prolactin (4.8–23.3)	6.5 ng/ml
α -Subunit (0.04–0.38)	0.09 ng/ml
Fasting insulin (0–29.1)	47.7 UIU/ml
HbA1c (4–6)	6.0%
Fasting glucose (60–99)	92 mg/dl
Glucose + 120 min (50–139)	133 mg/dl
Cholesterol (0–170)	164 mg/dl
HDL (>40)	46 mg/dl
LDL (0–109)	99 mg/dl
Triglycerides (0–100)	94 mg/dl

her for other co-morbid conditions related to obesity. She had a normal 2-h glucose tolerance test as well as a normal fasting lipid profile. Her fasting insulin levels were elevated.

Her pelvic ultrasound at the time showed a uterus that was large for age measuring 6.6 cm in length and 19 cc in volume. The antero posterior (AP) diameter of the uterine fundus was 1.9 cm. The AP diameter of the cervix was 1.4 cm. The endometrial stripe was normal in appearance, measuring 3 mm. The right ovary measured 1.7 cc, and the left was 7.5 cc in volume. A 2-cm follicle was present in the left ovary.

B.C. currently has no signs of raised intracranial pressure or pressure symptoms of the hypertrophied gland on the surrounding structures. At present we are continuing to treat the precocious puberty, mainly for psychosocial concerns because her mother was very worried that menses would exacerbate her behavioral issues.

Discussion

Leuprolide acetate (Lupron), a nonapeptide GnRH agonist, is the most commonly used agent to treat central precocious puberty. Its mechanism of action is to down-regulate the GnRH receptors of the pituitary and prevent FSH and LH secretion. GnRH is a decapeptide that is synthesized and stored in the arcuate nucleus in the medial basal hypothalamus. It is released in a pulsatile fashion. It acts on the anterior pituitary gonadotro-

tropes, which express the GnRH receptors, and causes secretion of LH and FSH from the pituitary into the circulation. Leuprolide is a super agonist and is more potent than GnRH. It has a high affinity for the GnRH receptors and has a longer half-life (up to 3 h after an im injection, as opposed to 3–4 min compared with endogenous GnRH). Bioavailability of the commonly used depot preparations is high. They initially cause a sharp increase in pituitary release of LH and FSH, which causes a rise in serum sex steroids within 3 d of initial treatment. This continuous stimulation of the pituitary GnRH receptors then leads to down-regulation of pituitary receptors for GnRH, thus suppressing the hypophyseal-gonadal axis. GnRH receptor agonists are commonly used for treatment of prostate cancer because in males, it leads to decrease in serum testosterone to castration levels. This happens in 4–6 wk. The dose of leuprolide has to be high enough and should be given consistently.

We wanted to understand the relationship of leuprolide and pituitary enlargement or pituitary tumors. Does leuprolide acetate play a role in the development of pituitary adenomas? Or does it cause any complications, such as pituitary hemorrhage, when given to patients with a pre-existing diagnosis of a pituitary adenoma.

Our clinical concern was accentuated by an observation of another patient in our practice who had been treated for central precocious puberty since age 16 months with different preparations of GnRH agonists. An MRI of the brain was normal before treatment for central precocious puberty. She developed sterile abscesses secondary to depot leuprolide injections. At age 2 yr she was switched to a different GnRH preparation called Histrelin. Three months later, she was switched to daily sc injections of leuprolide acetate due to unavailability of Histrelin in the market. At age 9 yr and 8 months, she had a Histrelin implant placed sc in accordance with an ongoing study in our practice. Two months later, she began complaining of frequent headaches and underwent a head MRI that showed a 4 × 5-mm pituitary microadenoma. She

continued on page 6

continued from page 5

continued on the study for a year, after which the implant was removed and no further therapy was given. She was monitored with yearly MRIs that showed no subsequent change in the size of the pituitary microadenoma. She remains asymptomatic as far as the pituitary tumor is concerned.

We found a few case reports of patients on leuprolide who subsequently were discovered to have a pituitary adenoma, although the circumstances at diagnosis were different from our case.

There are several case reports in the urology literature (1–3) describing pituitary apoplexy in patients who had been started on GnRH therapy for treatment of prostate cancer. Leuprolide acetate is used as an antiandrogen in hormone-dependent prostate tumors, to decrease testosterone and estrogen levels, thus helping in regression of tumors. One patient developed pituitary hemorrhage after a single injection of leuprolide (3), whereas another had this occur after therapy for 10 d (2). In all cases, the reports seem to suggest that the pituitary adenoma was preexisting. However, this is debatable because these patients did not have an MRI of the brain before initiation of treatment, mostly because they were asymptomatic. A patient with prostate carcinoma, who did not respond to leuprolide acetate depot injections with expected reduction of testosterone levels, was subsequently discovered to have a pituitary adenoma that was focally positive for LH and strongly positive for FSH on immunohistochemical stain (6). Furthermore, this patient un-

derwent transsphenoidal hypophysectomy but still did not have adequate response in terms of decrease in prostate-specific antigen levels. A repeat MRI showed residual adenoma.

As far as leuprolide causing an enlargement of the pituitary gland, a small study was published in 2000 (4) in which 12 girls (mean age 7.3 yr), with idiopathic central precocious puberty were followed. These patients had MRIs that were obtained before and after GnRH agonist therapy was started. When MRIs were obtained 18 months (mean) after GnRH agonist therapy, there was no difference in the length, height, width, volume, or sagittal cross-sectional area of the gland even though the children had excellent clinical response in terms of suppression of puberty. There were no case reports of apoplexy in children with underlying pituitary adenoma who were receiving GnRH agonist for precocious puberty.

Leuprolide acetate is now increasingly used for prostate carcinoma, *in vitro* fertilization techniques, endometriosis, uterine fibroids, and suppression of central precocious puberty. It is being tested for use in Alzheimer's disease, polycystic ovary syndrome, functional bowel disease, and even as a contraceptive. According to an article from *Expert Opinion on Investigational Drugs* 2007 (5), there is evidence of GnRH receptor expression in nonreproductive tissues like hippocampus and cortex of human brain. Hence, the use of GnRH agonists may have more complex effects than originally thought. We need to keep

that in mind when we start any patient on GnRH agonist therapy and monitor these patients very closely for the first 3–4 wk. Although most pediatric patients with central precocious puberty undergo imaging of the brain before therapy, this is not a common practice with patients receiving GnRH agonists for other indications. Furthermore, any symptoms of headache should be investigated closely. We do not know whether GnRH agonists primarily cause microadenomas especially when therapy is initiated for the first time. As more patients receive GnRH agonists and are followed with imaging studies, the issue of the relationship to the pituitary gland may become more defined.

References

1. Hernandez Morin N, Huet D, Hautecouverture M. [Two cases of non-functional gonadotroph adenoma pituitary apoplexy following GnRH-agonist treatment revealing gonadotroph adenoma and pseudopituitary apoplexy after GnRH administration.] *Ann Endocrinol (Paris)*. 2003; 64:227–231 (in French).
2. Ogan K, Berger M, Ball R. Gonadotropin releasing hormone analogue antiandrogen failure secondary to a pituitary adenoma. *J Urol*. 1998; 160:497–498.
3. Reznick Y, Chapon F, Lahlou N, Deboucher N, Mahoudeau J. Pituitary apoplexy of a gonadotroph adenoma following gonadotropin releasing hormone agonist therapy for prostatic cancer. *J Endocrinol Invest*. 1997; 20:566–568.
4. Van Beek JT, Sharafuddin MJ, Kao SC, Luisiri A, Garibaldi LR. Prospective assessment of pituitary size and shape on MR imaging after suppressive hormonal therapy in central precocious puberty. *Pediatr Radiol*. 2000; 30:444–446.
5. Wilson AC, Meethal SV, Bowen RL, Atwood SC. Leuprolide acetate: a drug of diverse clinical applications. *Exp Opin Investig Drugs*. 2007; 16:1851–1863.
6. Massoud W, Paparel P, Lopez JG, Perrin P, Daumont M, Ruffion A. Discovery of a pituitary adenoma following a gonadotropin-releasing hormone agonist in a patient with prostate cancer. *Int J Urol*. 2006; 13:303–304.



A Case of Lithium Toxicity and Hyperparathyroidism

Sonia Ralli Grewal, M.D. and Ellis Levin, M.D.

University of California, Irvine, Medical Sciences I-C240, Irvine, California

Introduction

Lithium carbonate is a widely used drug in the management of psychiatric disorders, particularly manic-depressive illness. The drug, however, concomi-

tantly affects many endocrine processes, including that of the thyroid, parathyroid, and water balance. We present a case of a patient who presented with lithium toxicity and persistent hypercalcemia.

Case Presentation

A 60-yr-old male with bipolar disorder presented with nausea, vomiting, and poor concentration for the past 5 d. He

continued on page 7

Table 1
Summary of Laboratory Values over Time

Time after initial presentation	Initial	1 month	3 months	5 months
Ca (mg/dl)	11.7	10.8	11.1	10.7
Ionized Ca (mmol/liter)	1.65	1.52		
Intact PTH (pg/ml)	202.7	93.0	127.3	50.6
Cr (mg/dl)	4.6	1.0	1.1	0.9

dual energy x-ray absorptiometry (DEXA) scan revealed a T score of -2.2 at the lumbar spine, and T scores of -1.4 and -1.8 at the left and right hips, respectively. A summary overlook of his laboratory values over time, while on cinacalcet, appears in Table 1.

Of note, his calcium and intact PTH levels appeared to normalize with time while on cinacalcet therapy. However, given that a parathyroid adenoma was identified, and the patient had undergone complications including renal stones and reduced bone density, the patient was referred for parathyroid adenoma resection with discontinuation of the cinacalcet. The patient tolerated the procedure well, and 1 month after the adenoma resection, his intact PTH levels remained between 10 and 20 pg/ml, and calcium levels remained between 9.0 and 9.5 mg/dl, all within normal limits.

Discussion

Lithium, as noted previously, is a drug commonly used to treat manic-depressive illness. Its association with nephrogenic diabetes insipidus, hypothyroidism, and hyperparathyroidism makes it of great concern to endocrinologists. In this discussion, we will focus primarily on the issue of lithium-associated hyperparathyroidism and hypercalcemia.

It should be noted that lithium is predominantly excreted by the kidneys. Its reabsorption follows that of sodium—*i.e.* retention of lithium occurs in situations of sodium retention, such as volume depletion, renal ischemia, congestive heart failure, and use of nonsteroidal antiinflammatory drugs, angiotensin-converting enzyme inhibitors, and diuretics, for example. Therefore, in these situations, an anticipated dose reduction of lithium is warranted to avoid toxicity (1, 2).

The mechanism of lithium-induced hypercalcemia is generally thought to occur via two mechanisms. One mechanism is by directly decreasing renal calcium excretion, which occurs independent of PTH. The second mechanism, and the one of greater concern

had been treated with lithium for the past 4 yr for bipolar disorder; for the past year, he had remained on a stable regimen of lithium 300 mg in the morning and 600 mg in the evening. Of note, he had recently been prescribed trimethoprim-sulfamethoxazole for a urinary tract infection, approximately 2 wk before presentation. On admission, the patient was found to have acute renal failure, with a creatinine of 4.2 mg/dl (baseline was normal 0.8–1.0). The patient denied edema, chest pain, shortness of breath, constipation, abdominal pain, headache, visual changes, and headaches.

His past medical history was significant for bipolar disorder, as described, as well as hypertension, hyperlipidemia, and prostate cancer (status: posttransurethral resection of the prostate several years prior, in remission at the time of presentation). Aside from lithium and trimethoprim-sulfamethoxazole as mentioned previously, he was also taking atenolol, hydrochlorothiazide, clonidine, terazosin, bupropion, simvastatin, and ibuprofen as needed for joint aches.

Initial physical examination revealed stable hemodynamics: temperature was 97.1 F, blood pressure 104/60, heart rate 55, respiratory rate 20, and oxygen saturation 98%. The patient was in no acute distress; alert; oriented to self, place, and year; but he had slight difficulty with recall. He had no evidence of any skin lesions or rash. Head, neck, cardiovascular, respiratory, and abdominal exams were within normal limits. Neurological exam revealed cranial nerves II–XII to be grossly intact, with normal strength and sensation in all extremities, but he had slight tremor on outstretched hands.

Initial laboratory evaluation revealed the following (wnl = within normal limits; [] indicates normal range):

- Na 132 mEq/liter
- K 4.9 mEq/liter

- Cl 101 mEq/liter
- Bicarbonate 23 mEq/liter
- BUN 67 mg/dl
- Cr 4.6 mg/dl (2 yr ago was 1.2)
- Glu 81 mg/dl
- Mg 2.2 mg/dl
- Phos 3.3 mg/dl
- Ca 11.7 mg/dl (2 yr ago was 10.7)
- Ionized calcium 1.65 mmol/liter
- Intact PTH 202.7 pg/ml
- Vitamin D 12.2 ng/ml
- SPEP/UPEP: negative
- Lithium 3.39 mEq/liter [0.6–1.2]
- TSH 1.63 uIU/ml
- Free T₄ 1.0 ng/dl
- LFTs: wnl (albumin 3.7)
- CBC: wnl
- Lipids: wnl
- Prostate-specific antigen <0.01

Lithium toxicity with acute renal failure and hypercalcemia was concluded, given the patient's acute presentation and laboratory evaluation. Lithium, hydrochlorothiazide, ibuprofen, and trimethoprim-sulfamethoxazole were discontinued immediately. The patient was aggressively hydrated via iv fluids and subsequently diuresed with furosemide. The creatinine level normalized to 0.9 mg/dl and the lithium level normalized to 0.53 mEq/liter over the next few days; his calcium levels, however, declined minimally, and remained near 11 mg/dl. As a personal emergency arose, the patient needed to leave the hospital at that time. As his acute symptoms had resolved and was able to tolerate oral fluid intake with adequate urine output, without apparent sequelae of hypercalcemia, he was initiated on cinacalcet therapy, 60 mg/d, and discharged home with close follow-up.

Subsequent workup and evaluation as an outpatient included a renal ultrasound demonstrating a small nonobstructing 4 mm right-sided renal stone; these results were confirmed by a subsequent computed tomography scan of the abdomen. A parathyroid sestamibi scan was consistent with a left parathyroid adenoma. A

continued on page 8

continued from page 7

to the endocrinology community, is via altered sensing at the calcium-sensing receptor. Lithium increases PTH release by increasing the set point at which calcium suppresses PTH release (3). It is reported that approximately 50–60% of patients on chronic lithium treatment have PTH levels above the normal range, yet with normocalcemia. In a study by Haden *et al.* (4), seven young normocalcemic women on chronic lithium treatment for a mean of 5 yr were found to have a higher set point for calcium at which PTH was suppressed: a serum ionized calcium of 1.26 mmol/liter in the lithium-treated, *vs.* 1.21 mmol/liter in untreated patients.

An estimated 10–25% of patients on chronic lithium treatment, however, develop hyperparathyroidism and hypercalcemia. Lithium may increase calcium and PTH levels within several weeks, but in the majority of people, levels are within normal range (3).

Whether the mechanism of lithium-associated hyperparathyroidism is via parathyroid hyperplasia or adenoma formation is unclear. The prevalence of parathyroid adenomas in patients on chronic lithium therapy, for example, is reported in a wide range, varying from approximately 50–90%, depending on the study. One generally accepted thought is that in many patients, lithium may merely unmask an otherwise indolent parathyroid adenoma, by resetting of the calcium sensing set point, as described above. Perhaps with longer durations of therapy, resetting of the calcium set point to cause higher levels of PTH release may allow for further growth of the adenoma and/or hyperplasia of the parathyroid gland (5, 6).

With lithium-associated hyperparathyroidism and hypercalcemia, the first line of treatment is usually discontinuation of lithium. If the duration of lithium treatment has been relatively short, on the order of a few weeks to months, calcium levels will likely normalize with this intervention alone. If the duration of lithium treatment is much longer, it may take several months for the calcium level to normalize, or it may never normalize.

Any other medications that may contribute to hypercalcemia or inhibit renal excretion of calcium, such as hydrochlorothiazide, nonsteroidal antiinflammatory drugs, and trimethoprim-sulfamethoxazole, for example, should be discontinued as well (3, 6).

Surgical management is indicated particularly when a parathyroid adenoma or hyperplasia is detected with concomitantly elevated PTH and calcium levels that do not normalize with lithium discontinuation. How long one must wait for calcium levels to normalize after lithium discontinuation is unclear, per the literature, varying from weeks to several months. The decision for further surgical intervention should be made on an individual basis, based on the degree of hypercalcemia, its sequelae, and any other medical issues that may encumber surgical management (2, 6, 7).

Of particular interest in the presented case was the use of cinacalcet as a temporizing measure to help control the hyperparathyroidism and hypercalcemia until further evaluation could be completed. Given the increased use of cinacalcet in recent years, particularly with secondary hyperparathyroidism in end-stage renal disease, questions arise as to the utility of cinacalcet in the management of lithium-induced hypercalcemia and hyperparathyroidism. In a case report by Sloand *et al.* (8), two patients with bipolar disorder were noted, who were on lithium for 15–30 yr, with lithium-induced hyperparathyroidism and stage 3 chronic kidney disease. Both patients were treated with cinacalcet 30–60 mg/d, resulting in normalization of serum calcium (10.8 and 11.0 to 9.9 and 10.3 mg/dl, respectively) and decline in PTH within eleven months. Gregoor *et al.* (9) noted three patients with chronic kidney disease ($\text{CrCl} \sim 35$ cc/min) and lithium-induced hyperparathyroidism. Cinacalcet resulted in normalization of serum calcium levels and reduced PTH levels. Shoback *et al.* (10) studied 22 patients with primary hyperparathyroidism and hypercalcemia—they were treated with 30–50 mg/d of cinacalcet for 15 d, with normalization of serum calcium in 21 d and reduction of PTH levels. However,

these studies do not specifically address the use of cinacalcet in patients with lithium-induced hyperparathyroidism who do not necessarily have kidney disease.

While discontinuation of lithium is a first-line intervention for lithium-induced hyperparathyroidism, it is a very difficult option in many patients with difficult-to-control psychoses who relapse without lithium therapy or are unable to tolerate other antipsychotic medications because of many associated adverse effects. Furthermore, though rare, there are case reports of patients who underwent parathyroid adenoma resection or partial gland removal, and had recurrence of hyperparathyroidism after restarting lithium treatment. Although repeat neck surgery in these patients has identified previously unrecognized parathyroid hyperplasia and adenomas, neck reexploration is not without adverse effects (11). In the above two instances, where either discontinuation of lithium is not feasible, or hyperparathyroidism recurs after parathyroid surgery with resumption of lithium, perhaps adjuvant medical therapy with an agent such as cinacalcet would be beneficial. Moreover, in patients in whom surgery is not an option for various reasons, such medical therapy may be quite useful. However, further studies specifically addressing these issues with the use of calcimimetics like cinacalcet in lithium-associated hyperparathyroidism and hypercalcemia are warranted before such therapy becomes widely adopted.

References

1. Okusa MD, Crystal LJ. Clinical manifestations and management of acute lithium intoxication. *Am J Med.* 1994; 97:383–389.
2. Wolf ME, et al. Lithium therapy, hypercalcemia, and hyperparathyroidism. *Am J Ther.* 1997; 4:323–325.
3. Mallette LE, Eichhorn E. Effects of lithium carbonate on human calcium metabolism. *Arch Intern Med.* 1986; 146:770–776.
4. Haden ST, Stoll AL, McCormick S, et al. Alterations in parathyroid dynamics in lithium-treated subjects. *J Clin Endocrinol Metab.* 1997; 82: 2844–2848.
5. Awad SS, Miskulin J, Thompson N. Parathyroid adenomas versus four-gland hyperplasia as the cause of primary hyperparathyroidism in patients with prolonged lithium therapy. *World J Surg.* 2003; 27:486–488.

continued on page 9

continued from page 8

6. Khandwala HM, Van Uum S. Reversible hypercalcemia and hyperparathyroidism associated with lithium therapy: case report and review of literature. *Endocr Pract.* 2006; 12:54–58.
7. Abdullah H, Bliss R, Guinea AI, et al. Pathology and outcome of surgical treatment for lithium-associated hyperparathyroidism. *Br J Surg.* 1999; 86:91–93.
8. Sloand JA, Shelly MA. Normalization of lithium-induced hypercalcemia and hyperparathyroidism with cinacalcet hydrochloride. *Am J Kidney Dis.* 2006; 48:832–837.
9. Gregoor PS, de Jong GM. Lithium hypercalcemia, hyperparathyroidism, and cinacalcet. *Kidney Int.* 2007; 71:470.
10. Shoback DM, Bilezikian JP, Turner SA, et al. The calcimimetic cinacalcet normalizes serum calcium in subjects with primary hyperparathyroidism. *J Clin Endocrinol Metab.* 2003; 88: 5644–5649.
11. Suda DA, Schlickman PW, Perry PJ. Letter to the editor: the clinical dilemma of lithium-induced hyperparathyroidism in a treatment responsive patient: a case report. *Ann Clin Psychiatry.* 2006; 18:131–132.

PHYSICAL THERAPY AND NUTRITION NEWS

Nutritional Management of Gestational Diabetes Mellitus



*Alenka Ravnik-List, MS, RD, CDE and Phyllis Kaskel, MA, RD, CDN
Clinical Nutrition Coordinator (A.R.-L.), Division of Endocrinology, Diabetes & Bone Disease, Department of Medicine, and Director (P.K.), Clinical Nutrition, Mount Sinai Hospital and Faculty, Department of Community and Preventive Medicine, Mount Sinai School of Medicine, New York, New York*

Introduction

Appropriate management of gestational diabetes mellitus (GDM) is crucial for ensuring optimal outcomes for both mother and baby. The majority of cases can be achieved with dietary approaches alone. Current recommendations for macronutrient distribution, caloric requirements, and proper maternal weight gain are conflicting and controversial because there are no specific guidelines regarding nutritional management of GDM.

The objective of this article is to offer some practical suggestions for medical nutrition therapy (MNT) for women with GDM.

GDM is defined as glucose intolerance with onset or first recognition during pregnancy (1). Approximately 7–14% of all pregnancies in the United States are complicated by GDM depending on the population studied and the diagnostic criteria employed (2). Treatment modalities include MNT, blood glucose monitoring, and pharmacological therapy when needed (3).

MNT is the primary therapeutic strategy for the management of GDM. The real challenge is to balance the needs of a healthy pregnancy while maintaining adequate blood glucose levels. The

American Diabetes Association recommends women with GDM receive MNT upon diagnosis. A registered dietitian (RD) who is a Certified Diabetes Educator (CDE) (3, 4) is specifically qualified to design meal plans for these patients.

Goals of MNT

- Provide adequate maternal and fetal nutrition to avoid low birth weight and macrosomia.
- Achieve and maintain normoglycemia without compromising nutrients, energy requirements or developing ketosis.
- Appropriate gestational weight gain and prevent excessive weight gain in obese women.
- Lifestyle changes that prevent the recurrence of GDM in subsequent pregnancies and delay/prevent the onset of type 2 diabetes (3, 4).

The ideal caloric requirement for patients with GDM has not been established, but it should be enough to promote adequate weight gain, control blood glucose, and avoid ketosis. In patients with normal pre-pregnancy body mass index (BMI), adding 300 calories during the second and third trimester is recommended (5) bringing total calories to 2200–2400/d.

For obese women (BMI >30 kg/m²), a 30–33% calorie restriction (~1700–1800 kcal/d) has been shown to reduce

blood glucose levels, maternal body weight, and triglycerides without developing ketonemia (2, 4–7).

In very restricted caloric diets (1200 kcal or 50% of calories) glycemic levels improve but ketonemia develops, and these levels are strongly discouraged (4, 8). Caution needs to be exercised when limiting calories, so nutrient intake is not compromised.

Carbohydrates are the primary nutrient affecting postprandial glucose levels and various theories on proper carbohydrate restrictions abound. One approach recommends low carbohydrate consumption (30–40% of total calories) with an increased fat content to 40%. This rationale is based on studies showing low carbohydrate intake reduces hyperglycemia, improves fetal outcomes, and requires fewer women needing insulin therapy (9, 10).

Another approach suggests carbohydrate content above 40% and a fat restriction of 20–30% with higher incidence of insulin use to achieve normoglycemia (9, 11). Restricting carbohydrates and increasing fat content of the meal for some pregnant women has been shown in some studies to increase the recurrence rate of GDM in subsequent pregnancies (12).

continued on page 10

continued from page 9

The recommended dietary allowance (RDA) establishes a minimum of 175 g carbohydrate per day for pregnant women (6). Equally important is carbohydrate timing and distribution. Carbohydrates should be spread over three meals and three snacks, spaced between 2 and 3 h, including one in the evening to prevent overnight starvation ketosis (5, 11, 13).

Restriction of 15–30 g at breakfast (13, 14) is due to carbohydrate intolerance and insulin resistance time. Breakfast should include starch and protein; refined cereals, fruits, juices, and milk may not be tolerated. Avoidance of simple sugars from the diet is widely accepted.

Use of nonnutritive sweeteners may help control carbohydrate intake, but The American Pregnancy Association has not recommended saccharin in pregnancy as it crosses the placenta and may remain in fetal tissue.

Meal plans should be culturally appropriate and tailored to individual preferences, taking into consideration the patient's habits, weight changes, blood glucose readings, and ketone levels (1).

Patient food records are a great tool and provide valuable information allowing the health care provider to assess actual caloric intake and the patient's ability to follow and understand the prescribed meal plan, and they may explain the reason for weight trend.

Monitoring blood glucose levels is essential for any health care practitioner treating women with GDM. It provides immediate feedback about the effects of the type and amount of foods eaten, empowers the woman to make decisions regarding blood glucose readings, and allows them to actively participate in achieving normal blood glucose levels. These monitors may help identify women who are restricting foods exces-

sively to avoid the initiation of insulin therapy.

The positive effect of exercise over blood glucose control makes it an ideal adjunct therapy to nutritional management and should be indicated as part of the meal plan in women capable of participating (3, 5) when medically appropriate.

When MNT is not enough to maintain blood glucose levels, a pharmacological approach is required (1, 2), but nutritional management remains equally important and must be balanced with the chosen medication.

Most women with GDM revert to normoglycemia after delivery but are at higher risk for developing GDM in subsequent pregnancies and for developing type 2 DM later in life (1–3, 5). Therefore, women with GDM present an ideal group for diabetes prevention as they are motivated to do what is best for their babies and the behavioral changes may continue beyond pregnancy.

Conclusions

MNT plays a significant role in the treatment of GDM, but there are a lot of controversies regarding the appropriate nutritional approach.

Women with GDM should receive dietary education to promote healthy food choices to achieve normoglycemia during pregnancy and that will persist beyond the pregnancy. Diets should be individualized, culturally sensitive, and based on the continuous assessment of clinical indicators such as blood glucose readings, food records, ketonuria, and weight gain.

Choosing to prescribe diets low in carbohydrate over low fat not only puts patients at risk for ketosis, but may send conflicting messages to a population at increased risk for CVD and type 2 diabetes. Especially because the majority of women with GDM belong to

at-risk populations whose diets are grain based and the introduction of a low carbohydrate diet may be adverse to their culture.

References

1. Metzger BE, Coustan DR. Summary and recommendations of the Fourth International Workshop-Conference on Gestational Diabetes Mellitus. The Organizing Committee. *Diabetes Care*. 1998; 21(Suppl)2:B161–B167.
2. Gestational diabetes mellitus. *Diabetes Care*. 2003; 26(Suppl 1):S103–S105.
3. Metzger BE, Buchanan TA, Coustan DR, de Leiva A, Dunger DB, Hadden DR, Hod M, Kitzmiller JL, Kjos SL, Oats JN, Pettit DJ, Sacks DA, Zoupas C. Summary and recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus. *Diabetes Care*. 2007; 30(Suppl)2: S251–S260.
4. Knopp RH, Magee MS, Raisys V, Benedetti T. Metabolic effects of hypocaloric diets in management of gestational diabetes. *Diabetes*. 1991; 40 (Suppl)2:165–171.
5. American Diabetes Association. Evidenced-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. *Diabetes Care*. 2002; 25:s50–s60.
6. American Diabetes Association, Bantle JP, Wylie-Rosett J, Albright AL, Apovian CM, Clark NG, Franz MJ, Hoogwerf BJ, Lichtenstein AH, Mayer-Davis E, Mooradian AD, Wheeler ML. Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association. *Diabetes Care*. 2008; 31(Suppl)1:S61–S78.
7. Langer O. Management of obesity in GDM: old habits die hard. *J Matern Fetal Neonatal Med*. 2008; 21:165–171.
8. Knopp RH, Magee MS, Raisys V, Benedetti T, Bonnet B. Hypocaloric diets and ketogenesis in the management of obese gestational diabetic women. *J Am Coll Nutr*. 1991; 10:649–667.
9. Jovanovic L. Achieving euglycaemia in women with gestational diabetes mellitus: current options for screening, diagnosis and treatment. *Drugs*. 2004; 64:1401–1417.
10. Jovanovic-Peterson L, Peterson CM. Dietary manipulation as a primary treatment strategy for pregnancies complicated by diabetes. *J Am Coll Nutr*. 1990; 9:320–325.
11. Langer O, Hod M. Management of gestational diabetes mellitus. *Obstet Gynecol Clin North Am*. 1996; 23:137–159.
12. Moses RG, Shand JL, Tapsell LC. The recurrence of gestational diabetes: could dietary differences in fat intake be an explanation? *Diabetes Care*. 1997; 20:1647–1650.
13. Jovanovic L. Medical nutritional therapy in pregnant women with pregestational diabetes mellitus. *J Matern Fetal Med*. 2000; 9:21–28.
14. Gunderson EP. Intensive nutrition therapy for gestational diabetes. Rationale and current issues. *Diabetes Care*. 1997; 20:221–226.



Testicular Adrenal Rest Tumors in Congenital Adrenal Hyperplasia

Arlene Uy, M.D. and Theodore Mazzone, M.D.
University of Illinois at Chicago, Section of Endocrinology,
Diabetes & Metabolism, Chicago, Illinois

Introduction

The presence of testicular tumor in a male patient with congenital adrenal hyperplasia (CAH) was first described by Wilkins *et al.* in 1940 (1). These tumors are thought to arise from aberrant adrenal cells in the testes that are stimulated by ACTH, and are called testicular adrenal rest tumors (TART). Tumors increase in size during periods of sustained elevation of plasma ACTH levels. Prevalence of these tumors has been reported to vary between 27 and 47% of male patients with CAH (2). We report a case of a young adult man with CAH and bilateral testicular tumors that regressed with intensified glucocorticoid therapy.

Case History

A 32-yr-old man with congenital adrenal hyperplasia due to 21-hydroxylase deficiency presented to our clinic with bilateral scrotal masses. He had been diagnosed with classic salt-wasting CAH since birth and had irregular compliance with his medications, which included prednisone 7.5 mg daily and fludrocortisone 0.1 mg daily. He had just gotten married and had been trying to conceive a child. Physical examination was unremarkable except for bilateral multinodular testes. Ultrasound showed nodularity and heterogeneity in both testes. Left testis measured $4.1 \times 2.5 \times 4.2$ cm, and right testis measured $4.1 \times 3.7 \times 2.5$ cm. Serum AFP and β -HCG were negative. Serum ACTH and 17-OH progesterone were elevated at 90 pg/ml (reference range 7–69 pg/ml) and 20,580 ng/dl (reference range 120–520 ng/dl), respectively. Serum DHEA-S was 33 μ g/dl (reference range 160–449 μ g/dl). Electrolytes and testosterone levels were within normal range. Semen analysis revealed oligoazoospermia.

Our provisional diagnosis was bilateral testicular adrenal rest tumors. We recommended surgical biopsy and removal, but the patient refused. We attempted to shrink the tumors and increase the sperm count by manipulating his glucocorticoid regimen and improving medication compliance. Dose of prednisone was increased to 10 mg daily for 3 months, and the testicular tumors shrunk. Serum ACTH and 17-OH progesterone levels decreased to 7 pg/ml and 98 ng/dl, respectively. We resumed his previous regimen of Prednisone 7.5 mg daily and reinforced medication compliance. His sperm count rose and he stored his semen at the fertility clinic. He was eventually successful in conceiving a child.

Discussion

Testicular nodules caused by expanding adrenal rests have been recognized for many years in male patients with congenital adrenal hyperplasia. At wk 5 of embryonic life, the adrenal glands develop in the immediate vicinity of the gonads, and their separation does not occur until the adrenal groove becomes prominent. Before this phase, adrenal cortical tissue may adhere to the gonads. This aberrant adrenal tissue may descend with the testis (3). Adrenal rests within the testis occur in 7.5–15% of neonates and normally regress in early infancy (4). However, these cells can persist and proliferate in conditions of high ACTH, including Nelson's syndrome, Cushing's disease, Addison's disease, and CAH (5).

Testicular adrenal rest tumors resemble Leydig cell tumors with features on electron microscopy consistent with steroid secreting cells (6). The adrenal-specific enzyme CYP11B1 (11 β -hydroxylase) had been described in the

tumor tissue of a CAH patient (7). The concentration of the adrenal-specific steroid 21-deoxycortisol in the spermatic veins was found to be significantly higher than in the peripheral blood samples, suggesting local production of these steroids in the testes. The presence at the mRNA level of 11 β -hydroxylase and of ACTH and angiotensin II receptors in these tumors confirmed their strong relation to adrenal tissue (8).

These tumors are often seen in CAH patients with poor hormonal control and high ACTH levels, suggesting that ACTH is a dominant factor in tumor growth (9). However, in several studies, no direct correlation was found between ACTH levels and tumor growth (10). It has been hypothesized that angiotensin II may play a role in tumor development. Angiotensin II has a strong trophic effect on the adrenal gland, especially on the zona glomerulosa (11). Inhibition of angiotensin II production by angiotensin-converting enzyme inhibitors significantly decreased adrenal weight, implicating angiotensin II as an important factor in stimulation of adrenal growth (12). Thus, tumor growth in CAH patients may be stimulated not only by elevated ACTH concentrations but also by elevated angiotensin II levels, which are present in poorly controlled salt-wasting CAH patients.

The tumors are almost always bilaterally present and have benign histologic features, but because of their location in the mediastinum testis, they can lead to obstruction of the seminiferous tubules leading to gonadal dysfunction and infertility. In addition to these mechanical effects, androgenic steroids produced by the tumor may reach the circulation, interfering with the secre-

continued on page 12

tion of FSH and LH by the pituitary (13).

Glucocorticoid therapy with suppression of ACTH secretion is not always successful in reducing tumor size (8). Claahsen-van der Grinten *et al.* (14) evaluated the effects of testis-sparing surgery in eight adult males with CAH and found no improvement in testicular function 22 months after surgery. Peritubular fibrosis and tubular hyalinization was seen in testes biopsy specimen taken during surgery, which confirmed irreversible damage of the testes probably caused by longstanding mechanical obstruction in all patients. Further studies are needed to investigate whether surgery at an earlier stage can prevent permanent testicular damage.

Conclusion

The presence of testicular adrenal rest tumors (TART) is associated with infertility in adult males with congenital adrenal hyperplasia. Regular testicular examination is therefore very important in the care of these patients. We describe a case of a young adult man with CAH and TART who had successful response to intensified glucocorticoid

therapy with tumor size reduction and increased sperm count.

References

1. Wilkins L, Fleishmann W, Howard JE. Macrogenitosomia precox associated with hyperplasia of the androgenic tissue of the adrenal and death from corticoadrenal insufficiency. *Endocrinology*. 1940; 26:385–395.
2. Stikkelbroeck NMML, Otten BJ, Pasic A, Jager GJ, Sweep CGJ, Noordam K, Hermus ARMM. High prevalence of testicular adrenal rest tumors, impaired spermatogenesis, and leydig cell failure in adolescent and adult males with congenital adrenal hyperplasia. *J Clin Endocrinol Metab*. 2001; 86:5721–5728.
3. Dahl EV, Bahn R. Aberrant adrenal cortical tissue near the testis in human infant. *Am J Pathol*. 1962; 40:587–598.
4. Sullivan JG, Gomel M, Kinder RB. Ectopic adrenocortical tissue found at groin exploration in children: incidence in relation to diagnosis, age and sex. *BJU Int*. 2005; 95:407–410.
5. Bercovici JP, Fiet J, Gibault L, Volant A, Abalain JH, Floch HH, Sonnet E, Fournier G. Testicular adrenal rest tumours in salt wasting congenital adrenal hyperplasia (in vivo and in vitro studies). *J Steroid Biochem Mol Biol*. 2005; 93:67–72.
6. Srikanth MS, West BR, Ishitani M, Issacs HJ, Applebaum H, Costin G. Benign testicular tumors in children with congenital adrenal hyperplasia. *J Pediatr Surg*. 1992; 27:639–641.
7. Clark RV, Albertson BD, Munabi A, Cassorla F, Aguilera G, Warren DW, Sherins RJ, Loriaux DL. Steroidogenic enzyme activities, morphology and receptor studies of a testicular adrenal rest in a patient with congenital adrenal hyperplasia. *J Clin Endocrinol Metab*. 1990; 70:1408–1413.
8. Claahsen-van der Grinten HL, Otten B, Sweep F, Span P, Ross A, Meuleman E, Hermus A. Testicular tumors in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency show functional features of adrenocortical tissue. *J Clin Endocrinol Metab*. 2007; 92:3674–3680.
9. Cabrera M, Vogiatzi M, New M. Long term outcome in adult males with classic congenital adrenal hyperplasia. *J Clin Endocrinol Metab*. 2001; 86:3070–3078.
10. Stikkelbroeck NMML, Hermus ARMM, Suliman HM, Jager GJ, Otten BJ. Asymptomatic testicular adrenal rest tumors in adolescent and adult males with congenital adrenal hyperplasia: basal and follow-up investigation after 2.6 years. *J Pediatr Endocrinol Metab*. 2004; 17:645–653.
11. McEwan PE, Vinson GP, Kenyon CJ. Control of adrenal cell proliferation by AT1 receptors in response to angiotensin II and low-sodium diet. *Am J Physiol Endocrinol Metab*. 1999; 276:303–309.
12. Chatelain D, Montel V, Dickes-Coopman A, Chatelain A, Deloof S. Trophic and steroidogenic effects of water deprivation on the adrenal gland of the adult female rat. *Regul Pept*. 2003; 110:249–255.
13. Dominguez OV. Biosynthesis of steroids by testicular tumors complicating congenital adrenal hyperplasia. *J Clin Endocrinol Metab*. 1961; 79:1390–1394.
14. Claahsen-van der Grinten HL, Otten B, Takahashi S, Meuleman E, Hulsbergen-van de Kaa C, Sweep F, Hermus A. Testicular adrenal rest tumors in adult males with congenital adrenal hyperplasia: evaluation of pituitary-gonadal function before and after successful testis-sparing surgery in eight patients. *J Clin Endocrinol Metab*. 2007; 92:612–615.



Case Report

Late Presentation of Thyrotoxicosis from Functioning Metastases in Metastatic Thyroid Carcinoma

Margaret Ryan, M.D., Fellow, Kevin Furlong, D.O., and Serge Jabbour, M.D.

Division of Endocrinology, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania

Introduction

A 60-yr-old female was admitted to our hospital with spinal cord compression. She had a history of metastatic follicular thyroid cancer diagnosed 7 yr previously, and her status was posttotal thyroidectomy, several rounds of radioactive iodine treatment, and chemotherapy. During this hospitalization, she underwent surgery for tumor resection, spinal decompression, and spinal fusion. Her postoperative course was complicated by the development of supraventricu-

lar tachycardia with a heart rate in the 190s.

The patient was on L-T₄ 112 µg daily at the time of her admission and had been maintained on this dose for over 1 yr before this admission. Her thyroid function tests at the time of surgery showed a TSH of 0.03, a free T₄ of 3.5 (normal 0.6–1.6) and a free T₃ of 9.8 (normal 2.4–4.2). Thyroglobulin level at that time was 743 ng/ml. Her physical exam was remarkable for a weight of 51 kg, significant tachycardia, shortness of

breath, diaphoresis and a marked tremor in addition to cachexia. A technetium whole body scan completed before this admission showed multiple areas of increased activity in the thoracic and lumbar spine, multiple ribs, right hip and right femoral head. A computerized axial tomography scan of the chest done during the admission showed innumerable pulmonary metastases as well as the previously noted multiple spinal and rib metastases (see Figs. 1 and 2).

continued on page 13

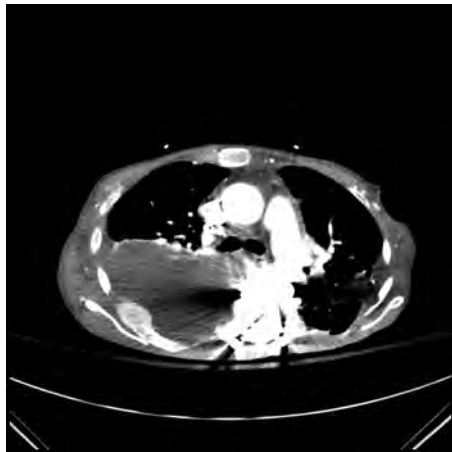


Figure 1. Rib metastasis with soft tissue extension and overlying pleural effusion.

L-T₄ was held and her supraventricular tachycardia converted back to sinus rhythm after several doses of adenosine. Despite withholding L-T₄, she remained clinically hyperthyroid for several days with tachycardia, tremors, and profuse diaphoresis, and her thyroid function tests remained elevated. She was eventually started on methimazole 10 mg daily, after which her hyperthyroid symptoms began to resolve. Repeat thyroid function tests performed 3 wk after initiation of methimazole treatment revealed an improvement of the hyperthyroidism, with TSH still suppressed at 0.03, and free T₄ and free T₃ within the normal range at 0.7 and 2.4, respectively. Eventually, the

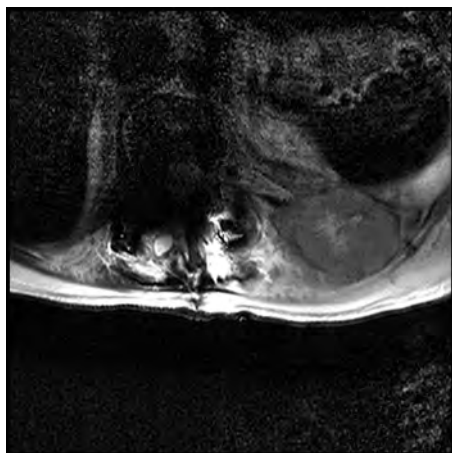


Figure 2. T11 spinal and paraspinal metastasis.

patient began to complain of increasing fatigue and low energy, and her TSH was repeated and found to be elevated at 7.28. Her dose of methimazole was decreased to 5 mg daily, and the patient was discharged home. At follow up 1 month after discharge, the patient continued on methimazole 5 mg daily and no L-T₄ replacement. She remained in normal sinus rhythm and denied any excessive diaphoresis. Her thyroid function tests at that time were TSH of 0.08, free T₄ of 1.2, and free T₃ of 5.7. At this time she was transferred to home hospice care.

Discussion

Thyroid carcinomas are typically non-functioning or hypofunctioning with poor iodine uptake and, therefore, are rarely associated with hyperthyroidism. It is possible to see thyroid cancer with thyrotoxicosis in patients with concomitant Graves' disease or, rarely, in a cancer presenting as a "hot nodule" where the cells have the malignant phenotype but still retain the ability for hormone synthesis. Activating mutations have been found in a small number of thyroid carcinomas and have been described in the *gsp* gene and in the TSHR gene (1).

The first report of a patient with functional thyroid carcinoma metastases was made in 1946 and since then there have been over 50 such reported cases (2). The vast majority of these reported cases have occurred in patients with follicular thyroid carcinoma, although there have been several reports of functioning metastases in insular, or poorly differentiated, as well as anaplastic carcinomas and there have been very rare reports of functional metastases of papillary thyroid carcinoma (3, 4). The severity of the hyperthyroidism is generally related to the overall tumor burden of the metastases as malignant thyroid tissue is generally much less efficient in the production of thyroid hormone than normal thyroid tissue

(5); previous studies have estimated the efficacy of iodine concentration in functioning metastases at about 10% of that of normal thyroid tissue (2). Metastatic thyroid carcinoma causing thyrotoxicosis has been reported most commonly in patients with bone and lung metastases and occurs more frequently in women.

In the patient described here, the thyrotoxicosis must be attributed to her metastatic lesions as she had undergone a total thyroidectomy several years previously. It is possible that her tumor cells retained the ability to produce thyroid hormone or contained an activating mutation from the outset, but the effect was minimal at the time of her initial thyroidectomy and only became clinically evident as the tumor burden rose significantly. Given the time course of her disease as well as the rapidity with which she seemed to convert from postsurgical hypothyroidism requiring L-T₄ replacement to thyrotoxicosis requiring antithyroidal medication, it also seems possible that one or more of her metastases had developed a new mutation leading to the autonomous production of thyroid hormone.

References

1. Russo D, Tumino S, Arturi F, Vigneri P, Grasso G, Pontecorvi A, Filetti S, Belfiore A. Detection of an activating mutation of the thyrotropin receptor in a case of an autonomously hyperfunctioning thyroid insular carcinoma. *J Clin Endocrinol Metab.* 1997; 82:735–738.
2. Ikejiri K, Furuyama M, Toru M, Muranaka T, Anai H, Takeo S, Sakai K, Saku M, Yoshida K. Carcinoma of the thyroid manifested as hyperthyroidism caused by functional bone metastasis. *Clin Nucl Med.* 1997; 22:227–230.
3. Girelli ME, Casara D, Rubello D, Pelizzo MR, Busnardo B, Ziliotto D. Severe hyperthyroidism due to metastatic papillary thyroid carcinoma with a favorable outcome. *J Endocrinol Invest.* 1990; 13: 333–337.
4. Tardy M. A case of hyperthyroidism due to functioning metastasis of differentiated thyroid carcinoma. *Ann Endocrinol (Paris).* 2007; 68:39–44.
5. Ober K, Cowan R, Sevier R, Poole GJ. Thyrotoxicosis caused by functioning metastatic thyroid carcinoma. *Clin Nucl Med.* 1987; 12:345–348.



FOUNDATION NEWS

EFF Announces the Grant Award Winners for the 2009 Spring Cycle

FELLOWS DEVELOPMENT RESEARCH GRANT PROGRAM IN DIABETES, OBESITY, AND FAT CELL BIOLOGY

This new research grant is supported by an unconditional educational grant from Amylin Pharmaceuticals, Inc. and provides for clinical grants in the area of cardiometabolic disorders in obesity and diabetes. Six grants have been awarded for the 2009 Spring Cycle in the amount of \$20,000.00 each.

Abdul-Razzak Alamir, M.D.—University of Florida College of Medicine, Jacksonville

“The Effects of Niacin on apo A-1 Gene Expression and HDLc Synthesis”
Program Director, Kent Wehmeier, M.D.

Brian T. Layden, M.D., Ph.D.—Northwestern University Feinberg School of Medicine

“The Role of Free Fatty Acid Receptor-2 in Proliferation of Pancreatic β Cells”
Program Director, Peter Kopp, M.D.

Kerri L. Marquard, M.D.—Washington University School of Medicine

“Oocyte/Granulosa Cell Communication in an Insulin Resistant Mouse Model”
Program Director, Kelle Moley, M.D.

Dorothee Kim Dang Newbern, M.D.—Duke University

“BCAA and Pathogenesis on Insulin Resistance”
Program Director, Deanna Adkins, M.D.

Anisha D. Patel, D.O.—Yale University Medical School

“Obesity and Metabolic Changes Associated with Transgenic Marshmallow Mice”

Program Director, Thomas Carpenter, M.D.

Danielle E. Weiss, M.D.—Stanford Hospital

“Investigation of Potential Hormonal Basis for Sexual Dimorphism in Adipose Cell Size and Abdominal Fat Distribution”

Program Director, Laurence Katznelson, M.D.

MARILYN FISHMAN GRANT FOR DIABETES RESEARCH

This new research grant, named in honor of EFF’s long-time executive director, is funded through an unconditional education grant from the partnership of Bristol-Myers Squibb and AstraZeneca International and is limited to studies involving type 2 diabetes. Six grants have been awarded for the 2009 Spring Cycle in the amount of \$15,000.00 each.

Mandeep Brar, M.D.—University of Colorado, Denver

“Vascular Injury by Lipoproteins, Oxidants and Diabetes”
Program Director, Daniel Bessesen, M.D.

Constantine S. Djedjos, M.D.—Johns Hopkins University

“Hormonal Regulation of Hepatic Gluconeogenesis”
Program Director, Sally Radovick, M.D.

Clare Flannery, M.D.—Yale University

“The Effect of Hyperinsulinemia on Endometrium”
Program Director, Silvio Inzucchi, M.D.

Radha Nandagopal, M.D.—NICHD, National Institutes of Health

“Partners for Better Health in Adolescent Type 2 Diabetes: The Buddy Study”

Program Director, Constantine Stratakis, M.D.

Melinda Penn, M.D.—Children’s Hospital of Philadelphia

“The MicroRNA Expression of the Human β -Cell”

Program Director, Andrea Kelly, M.D.

Geoffrey A. Walford, M.D.—Massachusetts General Hospital

“Metabolite Signature of Normoglycemic Subjects with High and Low Genetic Risk of Developing Type 2 Diabetes Following Sulfonylurea Challenge”

Program Director, Beverly M. K. Biller, M.D.

THE EFF ENDOCRINE RESEARCH GRANT

This grant is for general endocrine topics, including, but not limited to, thyroid, bone, adrenal, pituitary, growth, and reproductive disorders. Three grants have been awarded for the 2009 Spring Cycle in the amount of \$7,500.00 each.

Ronadip R. Banerjee, M.D., Ph.D.—Stanford University

“Investigating the Basis of Increased Diabetes Risk from Postnatal Growth Restriction”

Program Director, Laurence Katznelson, M.D.

Deirdre A. Conway, M.D.—University of California, Los Angeles

“Evaluating the Quality of Gamete Formation from Pluripotent Cells”

Program Director, Gautum Chaudhury, M.D., Ph.D.

continued on page 15

continued from page 14

Sheng Wu, Ph.D.—Johns Hopkins University

“The Roadmap from Obesity to Infertility”

Program Director, Sally Radovick, M.D.

Cycle 2, Fall 2009 Research Grant Applications

The new on-line research grant application process will be available at the end

of June 2009 for Cycle 2, Fall 2009 grant applications. Please see the EFF web site, www.endocrinefellows.org, for more information.

EFF Spring 2009 Preceptorial in Metabolic Bone Diseases

The EFF Preceptorial in Metabolic Bone Diseases will be held May 27–June 5, 2009, at Columbia University, College of

Physicians and Surgeons, New York, NY. Ten fellows were selected to participate in this in-depth program covering bone mass measurement techniques, application of calciotropic hormones, and metabolic bone marker measurements to evaluation and therapy, bone biopsy with histomorphometric analysis, and the most recent advances in the therapeutics of bone disorders. Support for the preceptorship is being given by Amgen, Novartis Pharma, and sanofi-aventis.



Contribute to *EndoTrends* . . .

Submit a patient case study, journal review, or research update to *EndoTrends*, an innovative, quarterly newsletter for endocrine fellows sponsored by the Endocrine Fellows Foundation (EFF). In each issue, we seek to provide practical clinical information on a variety of topics.

The Endocrine Fellows Foundation realizes that, as dedicated medical practitioners, our mentors and peers are our best resource for growth and education. Endocrine Fellows are encouraged to submit ideas and/or articles for publication and will receive a \$300 honorarium for accepted material.

Articles should range from 800–1000 words or two to four typewritten pages. Exceptions for longer or shorter articles may be made based on content. Submissions should include an original manuscript (including all applicable bibliographic references), a diskette containing the article (Word preferred, ACSII format also accepted), plus any accompanying photographs, charts, or graphs (graphic accompaniment to submitted articles is highly encouraged).

Figures should be submitted as TIFF or EPS files. Photoshop files are also acceptable. Please submit artwork at the size it should be printed. See <http://cjs.cadmus.com/da> for additional information. Please provide a good quality hard copy for each figure submitted. Please send figures on CD or disk rather than e-mail.

Please note: EFF reserves the right to edit the material as necessary to accommodate the available space. **Your Mentor must review, approve, and sign off on your articles before you submit them to our office.**

If you have a topic that you think would be of interest to our readers, please forward your submission to the Endocrine Fellows Foundation, c/o Association Resources, 1310 19th Street NW, Washington, DC 20036. For questions, please call (877) 877-6515 or fax 860-586-7550.