



Case Report

## The Houssay Phenomenon in a Pediatric Patient with Type 2 Diabetes

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### Clinical Presentation

In 2002, at the age of 10, our patient presented with new-onset diabetes. Her history at that time included a 2-wk history of polyuria, polydipsia, day and night enuresis, and 2 d of blurry vision. She had had a 20-lb weight gain over the summer despite being put on a diet by her mother. She reported being more tired overall and had some abdominal pain that was relieved with Pepto-Bismol. She denied headaches, diarrhea, emesis, and constipation. Her family history was notable for multiple family members with diabetes including both type I (mother) and type II (father, maternal aunt, maternal grandmother, maternal grandfather, paternal grandfather). Physical exam at presentation was remarkable for a weight of 56.7 kg (>97%) with a body mass index (BMI) of 26.5 (>97%). She was well appearing with moist mucous membranes and no evidence of respiratory distress. There was no abdominal tenderness. She was oriented to person, place, and time and interacted appropriately with all staff. Her neurologic exam was unremarkable. Laboratory analysis at that time demonstrated a serum glucose of 415 with a bicarbonate of 23. Her venous pH at that time was 7.36. Autoantibody studies were performed including anti-glutamic acid decarboxylase and islet cell antibodies, and both were negative. An insulin level at presentation was 6.4. She was started on a regimen of lantus (18 U at bedtime) and lispro (6 U with meals plus sliding scale).

She continued to have poor control and poor compliance with follow-up. During the first year, metformin (500 mg) was also added to her regimen and increased from daily to twice daily dosing. At that time she was lost to follow-up for 2 yr. On her return to clinic in 2004, she continued to have poor control, although she had had some significant weight loss and now weighed 48.2 kg (73%). She reported that her medical regimen had been continued and followed by her primary care provider. Despite the weight loss, she continued to have an elevated A1c of 11.7%. Autoantibody studies were repeated and were again negative, including thyroid antibodies. At this visit, she was transitioned to a 70/30 insulin regimen (10 U twice daily) with Novolog for additional corrections. Glucophage was discontinued as she was noncompliant with the medication.

She was then lost to follow-up for 3 yr. She returned to clinic in 2007 when she was having recurrent episodes of hypoglycemia. At that time, she reported low blood glucose in the morning and also around 1100 h. As she was having multiple episodes of blood sugars in the 40s–50s with symptoms, her primary care physician had discontinued all diabetes therapies. Despite discontinuation of insulin, she continued to have low blood sugars throughout the day. She did exercise at physical education at school and walked around the complex where her family lived; alto-

gether, she worked out for about 35 min/d for 5 d/wk. She had made no significant dietary changes. She had menarche at age 10 yr and continued to have regular menstrual periods since that time. At this visit she had a BMI of about 23 and some weight gain since her previous clinic visit; she remained at about the same percentile for weight. Laboratory results were obtained at this visit. Again, she demonstrated no evidence of anti-islet autoimmunity by antibody screening consistent with the diagnosis of type 2 diabetes and she continued to have detectable insulin levels (9.5). Her A1c at this time had dramatically improved to 6.2%. However, she was noted to have a low  $T_4$  in the presence of a normal TSH, suggesting the presence of central hypothyroidism.

Because of the concern for hypopituitarism, a 1- $\mu$ g ACTH stimulation test was obtained with the following results on 17 May 2007:

1640 h: Cort-S—16.1  $\mu$ g/dl (60 min after ACTH)

1620 h: Cort-S—17.6  $\mu$ g/dl (40 min after ACTH)

1600 h: Cort-S—15.1  $\mu$ g/dl (20 min after ACTH)

1540 h: Cort-S—7.0  $\mu$ g/dl (pre-ACTH administration)

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## LETTER FROM THE PRESIDENT

As incoming president of the Endocrine Fellows Foundation, I'd like to welcome all of you to an exciting new year of programming and initiatives and take this opportunity to both look back at the past year and look ahead to significant change in the coming years. 2008 saw the well-deserved retirement of our long-time executive director, Marilyn Fishman, as well as the transition of EFF leadership. Sherm Holvey, the president and guiding force behind EFF since its inception 20 years ago, has stepped down from the presidency of EFF. He will remain on our board, directing efforts to secure funding for future educational and research initiatives as liaison to our Corporate Advisory Council. We all deeply appreciate Sherm's and Marilyn's efforts, which allowed EFF to grow and prosper over the past two decades. 2009 is a year of change and challenge for all of us. Our headquarters is now appropriately in Washington, DC; your new EFF president fittingly hails from Chicago; and our organization is now under the executive direction of Anne Mercer. I encourage all of you to get to know Anne in the coming year. David Kendall, an initial EFF fellow and now a widely respected investigator in diabetes at the International Diabetes Center, has joined our board and we welcome his energy, enthusiasm, and insight.

Despite the challenges all organizations, whether non-profit, corporate, or academic, face in 2009, EFF has been successful in securing funding for new programming, thanks to the generosity and vision of companies such as Amylin, Takeda, Merck, and Bristol-Myers Squibb. And also, despite the perceived awkward relationship between the pharmaceutical industry and academic and educational organizations, our corporate partners share our vision of creating a new generation of thought leaders and investigators in endocrinology and metabolism. Recent unrestricted grants have allowed us to greatly expand our research grant

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### Letter from the President

programming, which we believe is a critical component of launching a fellow's long-term career. As outlined on the *Foundation News* page, we now have funding for research grants that extend into the first 2 years post-fellowship, a key transitional phase in future academic success. We look forward to meeting many of you at our fellow's forum in June prior to the ADA meeting. In the coming months, we will keep you apprised of the many new didactic and interactive educational programs that will be appearing on our web site.

The next few years will continue to present challenges as we try to continue to succeed in a vexing new economic world. The success of our organization largely depends upon your continued participation, but even more so upon your personal career success as you move forward. I, and the board of EFF, look forward to meeting all of you in the coming year.

Sincerely,  
Mark Stolar, M.D.  
President

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### The Housay Phenomenon in a Pediatric Patient with Type 2 Diabetes

1540 h: ACTH—17 pg/ml

1540 h: TSH—2.16  $\mu$ U/ml (nl 0.30–5.00);  
FT<sub>4</sub>—0.39 ng/dl (nl 0.6–1.8)

Based on these data, magnetic resonance imaging of the brain was performed and demonstrated a large hyperintense cyst-like lesion of the pituitary gland. The lesion impinged upon the inferior surface of the optic chiasm.

She was subsequently referred to neurosurgery where operative excision of the lesion was performed. Based on his-

tologic and operative findings, diagnoses of craniopharyngioma or Rathke's pouch cyst were considered. She later had recurrence of headaches and expansion of the lesion, which was most consistent with the diagnosis of craniopharyngioma. Once started on hydrocortisone replacement, she also had recurrence of her hyperglycemia and no further episodes of hypoglycemia.

#### Discussion

Although the presentation of intractable hypoglycemia in a patient with type 1 diabetes is a phenomenon well known

to pediatric endocrinologists, similar cases have not been described in the literature with respect to pediatric patients with type 2 diabetes. This young woman's case was complicated by a variety of factors including psychosocial barriers that manifest as poor follow-up and compliance.

Understanding the etiology of her hypoglycemic episodes begins with confirming the underlying pathogenesis of her diabetes because this knowledge informs the differential diagnosis. At

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initial presentation, she was hyperglycemic but nonketotic, a presentation that characterizes up to 50% of new-onset patients with type 1 diabetes. Her family history was very strong for type 2 diabetes, but her mother was also reported to have type 1, further confounding the diagnosis. However, she had no evidence of autoimmunity as detected by autoantibody assay at presentation. This was followed over the subsequent 5 yr, and no evidence of autoimmunity was ever detected. In addition, at 5 yr out from initial diagnosis, she continued to make near normal levels of insulin even after the discontinuation of injected insulin, suggesting maintenance of islet cell function that far exceeds the typical patient with autoimmune disease. Because patients with type 1 diabetes have a nearly 100-fold increase in risk for Addison's disease compared with the general population, verifying her diabetes etiology is a critical step in understanding her presentation (1).

A valuable clue in her initial evaluation was the laboratory evidence suggestive of central hypothyroidism. Although hypothyroidism itself is no longer thought to be a direct cause of hypoglycemic episodes, it can exacerbate an underlying tendency toward hypoglycemia. More importantly, testing for hypothyroidism is extremely efficient and is helpful in this kind of special case where there may be pituitary dysfunction but where polyglandular autoimmunity has still not been completely excluded. Based on this test, we were able to move quickly to a formal evaluation of pituitary function and to ultimately demonstrate the presence of a pituitary lesion.

The resolution of diabetes after injury to the anterior pituitary is commonly known as the "Houssay phenomenon," named eponymously for the Argentine physiologist and Nobel Laureate who demonstrated that diabetes in pancreatectomized dogs could be reversed by subsequent excision of the anterior pituitary (2). In humans, this phenomenon

has been repeatedly demonstrated in patients with Sheehan's syndrome, complicating pregnancy and parturition, and has also been described more rarely secondary to malignant infiltration of the pituitary (2–6). To our knowledge, this is the first description of this phenomenon in a pediatric patient with type 2 diabetes.

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# Congenital Hypothyroidism and Late-Onset Goiter

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## Introduction

Congenital hypothyroidism (CH) is a concerning diagnosis because of the imperative need to have thyroid hormone for the developing brain. The devastating outcome of patients without sufficient thyroid hormone is easily prevented by having adequate thyroid hormone replacement. Early detection has improved since the implementation of newborn screening exams. Primary CH can be transient or permanent. Transient CH can be secondary to exposure to anti-thyroid medication or transplacental transfer of anti-thyroid antibodies from the mother. These cases usually require treatment for up to 6 months with resolution. There are multiple etiologies of permanent CH. These include thyroid dysgenesis (aplasia, hypoplasia, or an ectopic thyroid gland), dyshormonogenesis, iodine deficiency, TSH receptor defect, and sodium-iodine symporter defect. The most common etiology worldwide of CH is iodine deficiency, whereas the most common etiology in developed nations is thyroid dysgenesis. The etiology of primary CH is important for prognosis and genetics as well as epidemiologically. Uncommonly, patients will present at birth with a goiter. Neonatal goiter most often suggests a diagnosis of dyshormonogenesis. We present a case where goiter developed 9 yr after diagnosis while on appropriate treatment of CH. Implications of such a case are discussed as well.

## Case Presentation

The patient is a 10-yr-old female with a history of CH who was referred for evaluation for goiter. She reported neck swelling that began 1 yr before presentation and progressively increased in size. She denied any associated pain, dysphagia, dyspnea, or hoarseness. Review of systems was negative for any hypoor hyperthyroid symptoms. Her mother denied any history of hearing deficits since birth.

The patient was the product of full-term gestation with significant maternal his-

tory of gestational diabetes that was controlled with diet alone. After delivery, the patient was in the neonatal intensive care unit for 24 h for concern of neck swelling that resolved without issues and she did well after discharge. Mom was notified that newborn screen was positive for hypothyroidism. At 2 wk of age, repeat labs confirmed diagnosis with TSH of 742  $\mu$ IU/ml (normal values 0.4–4.0  $\mu$ IU/ml) and total  $T_4$  ( $TT_4$ ) of <1.05  $\mu$ g/dl (normal values 4.8–19.0  $\mu$ g/dl). Treatment was initiated with L- $T_4$  37.5  $\mu$ g daily. After 10 d of treatment, repeat blood test showed TSH of 4.6  $\mu$ IU/ml (0.4–4.0  $\mu$ IU/ml),  $TT_4$  of 3.9 ng/dl; 4.8–19.0  $\mu$ g/dl). Her medication dose was titrated to keep pace with her growth and weight gain while maintaining normal levels of TSH and  $T_4$ . Throughout childhood, TSH was within the normal range and our patient did not demonstrate any clinical symptoms of hypothyroidism.

Approximately 1 yr before presentation to our clinic, patient did not have consistent monitoring of her thyroid function. Mom brought her to her primary pediatrician for evaluation of neck swelling. She did not have any outward symptoms of hypothyroidism. Blood test obtained by PMD at this time revealed TSH of 2.19  $\mu$ IU/ml (0.40–4.00) and free  $T_4$  ( $FT_4$ ) 1.5 ng/dl (0.8–1.9). Patient had been on the synthroid dose of 100  $\mu$ g for the past year and adherent with medication.

Physical exam at presentation revealed a normal heart rate of 84 beats/min, normal blood pressure of 86/52. Her height was 137 cm (41.96%, –0.20 sd) and weight was 31.3 kg (35.10%, –0.38 sd). Neck exam was significant for a grossly enlarged thyroid gland, with the right lobe (5 cm) larger than the left lobe (3 cm). The thyroid was diffusely enlarged, mobile, smooth, and soft. The gland was nontender and no lymphadenopathy was palpated. There was no bruit. The rest of

her physical exam was unremarkable. She has grown well, met developmental milestones, and does well in her age-appropriate grade level within the mainstream classes. She is very active and social.

Laboratory evaluation was significant for a TSH 9 mIU/liter (normal values 0.35–5.50 mIU/liter),  $FT_4$  1.1 ng/dl (normal values 0.8–1.9 ng/dl), thyroid peroxidase antibodies <15 IU/ml (normal <34.9 IU/ml), thyroglobulin antibody <20 IU/ml (normal <39.9 IU/ml, and TSH receptor binding antibody 10% (normal values <9% negative, 10–15% indeterminate, >16% positive).

Ultrasound of the neck showed a multinodular goiter with a right-dominant nodule. The right thyroid lobe measured  $6.27 \times 2.57 \times 2.90$  cm and left thyroid lobe measured  $5.81 \times 2.06 \times 2.48$  cm with an isthmus of 1.52 cm. There were multiple solid nodules within the right and left thyroid lobes with the largest nodule located on the right thyroid measuring 1.7 cm in diameter. No lymph nodes were noted on the ultrasound. Pathology from the fine needle aspiration biopsy of the gland was consistent with a follicular lesion.

An Iodine-123 uptake scan with perchlorate washout was performed after discontinuation of patient's levothyroxine for 14 d. Over this time period, the TSH increased to 102  $\mu$ IU/ml and  $FT_4$  decreased to 0.5 ng/dl. Our patient received 244  $\mu$ Ci of Iodine-123 via capsule followed by anterior and oblique radiographic scans of the thyroid gland. Initial uptake images demonstrated a well-defined photopenic area in the lower left lobe and a smaller photopenic area just superiorly. The thyroid gland was noted to be markedly enlarged with initial uptake of 52.3%. After 4 h, 180 mg perchlorate was administered and uptake was calculated at 30-min intervals for 4 h. Uptake after 1 h per

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chlorate administration was 3.1%. The dramatic reduction of uptake status postperchlorate administration was consistent with abnormal organification of iodine by the thyroid.

Our patient successively underwent a total thyroidectomy 8 wk after her initial presentation to our clinic. She did not have any complications with the procedure. The surgeons noted the thyroid gland to be large with gargantuan veins into the large thyroid gland. Total thyroid weight was 93 g. Pathology report showed multiple hyperplastic nodules and focal cytological atypia, consistent with dys hormonogenetic goiter. No carcinoma tissue noted.

She restarted her replacement levothyroxine at her previous dose after her iodine uptake scan and after approximately 14 d of treatment, TSH was 60.25  $\mu$ IU/liter and FT<sub>4</sub> was 0.7 ng/dl. Her dose was increased, and we will plan on titrating as necessary.

This case represents a case of thyroid dys hormonogenesis and its unusual presentation with late onset of a goiter while on appropriate hormone replacement. It warrants discussion based on the rarity of the presentation. At this time, we are in the process of determining the etiology of dys hormonogenesis.

## Discussion

This is a unique case of CH that presented with late development of a goiter

while on adequate thyroxine replacement therapy. The differential diagnosis of CH with goiter includes a large category of dys hormonogenesis with defects attributable to thyroid peroxidase (TPO) deficiency, thyroglobulin gene mutation, the sodium iodine symporter defect, Pendrin protein defect and thyroid oxidase 2 defects (1). The development of a goiter later in life has been reported in cases of CH with both mutations of TPO gene and Pendrin gene defects (2).

TPO is a glycosylated hemoprotein responsible for the iodination of tyrosine residues within thyroglobulin and for coupling these residues to form T<sub>4</sub> and T<sub>3</sub>. To date, more than 50 mutations in the TPO gene have been described with a variable decrease in TPO bioactivity. Together, these mutations are believed to be the most prevalent causes of inborn errors of thyroid hormone synthesis. There is a wide range of clinical presentation as well as varied level of biochemical inactivity (3).

Patients with Pendred syndrome have congenital deafness due to sensorineural hearing loss and goiter. The goiter usually develops later in life and is only at times associated with hypothyroidism. The underlying pathology is a mutation of the Pendrin gene that is normally expressed in the kidney, inner ear, and the apical border of the thyroid cell and functions to transport iodine into the follicular lumen.

Our patient is in the midst of a work up to evaluate the etiology of the dys hormonogenesis. It is not likely to be Pendred syndrome because she has normal hearing and more prominent clinical hypothyroidism. Because this patient developed goiter later in life, if she does have TPO mutation, it is important to remove the thyroid gland as there have been reported cases of thyroid cancer in such cases of dys hormonogenesis (4). It is unusual that our patient developed goiter while on adequate thyroxine replacement. This case raises distinct questions in its unusual presentation. Should we be evaluating our patients with CH and the presence of thyroid gland more thoroughly to evaluate for the etiology of dys hormonogenesis?

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Case Report

# Prader-Willi Syndrome and Its Multiple Endocrinopathies

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## Introduction

Prader-Willi Syndrome (PWS) is a genetic disorder that leads to multiple hypothalamic-pituitary abnormalities and resultant endocrinopathies. It is additionally characterized by obesity, the pathophysiology of which is altered from typical obesity.

## Case Presentation

H.L. is a 39-yr-old white male who is referred for evaluation of the endocrine issues related to PWS.

H.L. was diagnosed with PWS by genetic testing at the age of 24. He is obese; however, his weight had been stable until this

past year when he experienced a 10-lb weight gain. He moved into a new group home approximately 1 yr ago, and he notes that he's been allowed to eat more snacks at the new home. He complains of constant, insatiable hunger. He otherwise has no complaints, and specifically denies any fatigue, cold intolerance,

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constipation, or changes in body shape. He has no history of fractures; his dairy intake is minimal, and he is on no calcium or vitamin D supplements. He states that he spends most of his time playing video games and smoking cigars. He has been happy in his new group home; he has a girlfriend and he works part-time as a sales clerk. He has no other medical problems other than the PWS; he describes a right orchiectomy as a child. His family history is significant for diabetes mellitus type 2 in several members. His medications include paroxetine, furosemide as needed for peripheral edema, and fiber supplements.

On physical exam, H.L.'s weight is 225 lbs and his body mass index (BMI) is 38. His blood pressure is 142/62, and the rest of his vital signs are within normal limits. He demonstrates marked centripetal obesity. He has a thin beard; his thyroid is nonpalpable. His cardiovascular and pulmonary exams are normal. His abdomen is obese with a large, overhanging pannus. His penis is small, measuring 3 cm in length; his left testicle measures 1 ml and his right testicle is nonpalpable. He has trace peripheral pitting edema and is wearing compression stockings. On neurological examination he demonstrates a mild developmental delay.

On laboratory examination, his comprehensive metabolic panel is normal. His TSH is 1.55 mIU/ml and free T<sub>4</sub> 1.31 ng/dl. His IGF-I is 60 ng/ml. His total testosterone is 178 ng/dl, FSH 45 mIU/ml, and LH 6 mIU/ml. His 25OH vitamin D is 30 ng/ml; his DEXA T score is -2.2 at the lumbar spine and -1.1 at the left hip.

In summary, this is a 39-yr-old man with PWS who presents with recent weight gain. We performed a literature search from 1996–2007 to evaluate the following questions:

- 1) What endocrinopathies are associated with PWS, and what treatment options are available?
- 2) What is the pathophysiology of obesity in PWS, and what are the most effective means of weight management in these patients?
- 3) What is the mortality rate in patients with PWS, and what are the common causes of death?

## Overview of PWS

PWS was first described in the 1950s as a syndrome consisting of mental impairment, short stature, hypogonadism, and obesity. It shows no gender or ethnic preference, and it has an incidence of 1 in 25,000 births. A “PWS critical region” on the long arm of chromosome 15 has been identified, but the precise etiology is still unknown. Inheritance is subject to genomic imprinting, with paternal deletion of this region accounting for 70% of cases, maternal disomy 28%, and microdeletion of the imprinting center 2%. Major and minor diagnostic criteria were developed in 1993; however, today the diagnosis is commonly made by molecular testing performed in patients with a characteristic phenotype. This includes hypotonia with poor suck in infancy, followed by global developmental delay and hyperphagia. Classic physical exam findings include a narrow face, almond-shaped eyes, fair hair and skin, short stature, and small hands and feet (1, 2).

Several endocrine disorders are associated with PWS, including hypogonadism, obesity, abnormal body composition, GH deficiency, and osteoporosis, and we will review each of these in the following sections.

## Hypogonadism

The majority of patients with PWS have a dysfunctional hypothalamic-pituitary-gonadal axis, which manifests as delayed or incomplete sexual maturation. Both genders typically have hypoplastic external genitalia, and males often have undescended testes. Adult males have low serum testosterone levels and females have anovulatory cycles. This appears to be hypogonadotropic hypogonadism: investigators have found that repeated administration of GnRH improves LH secretion (3). There also appears to be a component of primary gonadal failure with poor spermatogenesis; male patients often have low testosterone and LH and elevated FSH levels (4). Sex hormone replacement is inconsistently prescribed, and unfortunately there have been no prospective trials assessing outcomes following testosterone administration. In theory, of course, sex hormone replacement might help with body composition,

bone density, and psychosocial status, and many authors recommend it be offered.

## Obesity and Hyperphagia

Neonates with PWS are typically underweight, and demonstrate hypotonia, poor suck, and feeding difficulties that lead to failure to thrive unless medical care is sought. This usually improves by about 9 months of age, and from ages 1–6 yr there is a rapid onset of hyperphagia and obesity that persists into adulthood (5). Adults with PWS demonstrate profoundly abnormal feeding behavior, characterized by food stealing, food obsessions, and hoarding of food. These patients also interestingly note reduced satiety after eating, increased pain thresholds, and decreased ability to vomit (2). As a result, in the absence of strict caloric restriction and monitoring, the majority of adults with PWS are obese.

Several peptide hormones involved in appetite and satiety appear to be altered in PWS when compared with weight matched controls. Ghrelin, an endogenous GH receptor ligand, is primarily secreted by the stomach. Ghrelin is an orexigenic agent, rising just before meals and falling postprandially. Polypeptide Y (PYY) is an anorexigenic hormone that rises postprandially, and can acutely reduce ghrelin levels. Several studies have shown that ghrelin levels are markedly elevated in the fasting state in patients with PWS; this is in direct contrast to otherwise healthy obese patients, who typically show suppressed ghrelin levels (6). Recently, Giminez-Palop *et al.* (7) looked at these hormone levels in seven subjects with genetically confirmed PWS and 16 BMI matched controls. In the postprandial state, the subjects with PWS had higher ghrelin levels and lower PYY levels than the controls.

With this knowledge there is hope that the insatiable hunger characteristic of PWS may someday be ameliorated with pharmaceuticals. One study so far has unfortunately been disappointing. Tan *et al.* (8) performed a double-blinded, placebo-controlled randomized crossover study on four patients with PWS.

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Administration of somatostatin suppressed fasting ghrelin levels to that of non-PWS men but did not alter caloric intake. Further studies involving chronic administration are underway.

## Body Composition

Numerous studies have consistently shown both significantly increased body fat, typically in the 40–50% range, and reduced lean body mass in PWS compared with obese controls. Several factors are thought to be involved. There is a reduced basal metabolic rate relative to body size; this is related to the abnormal body composition. One study showed an approximate 50% drop in energy expenditure in PWS patients compared with weight matched controls (9). There also is a reduced level of physical activity in patients with PWS, which is thought to be due to obesity, hypersomnolence (sleep apnea is highly associated with PWS), and poor muscle strength; this reduced energy expenditure, however, also contributes to the low basal metabolic rate (1).

Interestingly, although total percent body fat is elevated in patients with PWS, the distribution is different than that seen in typical obesity and may actually reduce the risk for traditional obesity-related comorbidities in patients with PWS. Whole body MRI has shown that adult females with PWS have significantly reduced visceral adiposity compared with obese controls (10). Despite profoundly elevated percentage of body fat and reduced physical activity levels, several recent studies have shown greater insulin sensitivity in PWS patients compared with weight-matched controls (10, 11). This is in contrast to findings from older studies, many of which found prevalence rates of diabetes in the 20–30% range. These earlier studies, however, were done before the institution of strict caloric restriction, which has helped with weight maintenance (see below), and many had a small sample size and were uncontrolled. In line with this new hypothesis that patients with PWS may have less visceral adiposity and greater insulin sensitivity, adiponectin levels also have been found to be higher in PWS patients than obese controls (10, 11). Adiponectin is an “adipokine” produced by adipocytes, but it is

inversely related to the amount of visceral adiposity. Low adiponectin levels are found in patients with type 2 diabetes mellitus, obesity and cardiovascular disease.

## GH Deficiency

Many studies indicate that patients with PWS have GH deficiency (GHD), with blunted GH responses to GHRH and arginine, and low IGF-I levels. Some controversy exists as to whether this is true GHD *vs.* an apparent GHD that simply reflects obesity. Several arguments seem to favor the former: children with simple obesity often have normal to slightly elevated IGF-I levels, whereas those with PWS tend to have low IGF-I. Indeed, GHD has been reported in normal weight children with PWS (1). The clinical features of PWS and GHD are similar, both characterized by short stature, obesity, reduced muscle mass and decreased bone density.

PWS is currently an FDA-approved indication for exogenous GH administration in children, and studies have shown an increase in longitudinal growth and an improvement in body composition, reviewed by Burman in 2001. In adults the use of GH is more controversial. Proposed benefits include an improvement in body composition and bone density. There has so far been just one randomized, placebo controlled trial of GH use in adults with PWS, by Hoybye *et al.* in 2003. After 12 months, body fat decreased by 2.5% ( $P < 0.01$ ) and lean-body mass increased by 2.2 kg ( $P < 0.5$ ) in the treatment group (12).

## Osteoporosis

Osteoporosis is noted as a clinical feature of PWS in many reviews, although this appears to be based on case reports. The low bone density is thought to occur as a result of the hypogonadism and GH deficiency, although an abnormality inherent to PWS may also be possible. Fracture risk may also be increased; one observational study in the orthopedic literature examined all 31 patients with PWS living in a residential home. Fourteen of these patients had suffered a total of 58 fractures (13). There have been no systematic studies of osteoporosis treatment in patients

with PWS. Most authors recommend calcium and vitamin D treatment in all patients with PWS along with a dual-energy x-ray absorptiometry scan, with treatment for osteoporosis to be guided by recommendations for the general population.

## Weight Management

The most successful weight maintenance programs for patients with PWS include extensive psychological and behavioral counseling, involving the patient, family, and caregivers. As previously discussed, patients with PWS have insatiable hunger, and will often hoard food or steal money to buy food. Patients with the most success live in group homes, where a low-calorie and well-balanced diet is administered along with regular exercise. Several recommended strategies include supervision at mealtimes, locking away food and money, and non-food-related awards (1). Because of the altered body composition with increased fat and decreased lean mass, patients with PWS need to restrict their calories further than the general population for weight maintenance. Several authors recommend restricting calories to 1000–1500 kcal/d (30% protein, 40% carbohydrate, and 30% fat) (14). Unfortunately, there have been no systematic studies of using either anorectic or antiabsorptive agents in patients with PWS, and avoidance of bariatric surgery is usually recommended due to concerns of ongoing hyperphagia and gastric rupture.

## Mortality

PWS is associated with an increased mortality rate, even when the intellectual disability is adjusted for (15). In 2001, Whittington *et al.* (16) estimated a death rate of 3% per year for PWS patients *vs.* 1%/yr for the general population. In children with PWS, the most common cause of death appears to be respiratory or infectious (17). In 2003, Smith *et al.* (18) reported on a series of 36 adults with genetically confirmed PWS. Ten deaths occurred over a period of 10 yr, with the average age of death 33 yr. The cause of death was cardiac in five, stroke in one, pulmonary embolism in one, hypoglycemia in one, pneumonia in one, and one was not determined.

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## Case Follow-Up

HL is a 39-yr-old white male with genetically confirmed PWS who presented with recent onset weight gain. It is likely that his weight gain is due to a recent relaxation in his caloric restriction. We spoke with his caregivers, who will resume his previous 1400 kcal/d diet. He was found to be hypogonadal, and he opted for testosterone replacement. He was also found to have a low IGF-I level, but he has declined any further work-up of GH deficiency due to a needle phobia. He also has osteopenia; we have started him on calcium and vitamin D supplementation.

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# Pituitary Adenomas

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## Introduction

This case report describes a 19-yr-old man who presented to the emergency room with headaches for 5 months and ultimately was diagnosed with acromegaly. The clinical presentation of acromegaly and treatment options will be discussed.

## Case Presentation

The patient is a 19-yr-old man who presented to the emergency department with brief, intermittent headaches and recurrent nosebleeds. Initially, the headaches lasted for a couple of hours, but the headaches were more severe on presentation. There was no associated weakness, numbness, or visual changes. He also noted six nosebleeds over the previous 3 wk; he did not have a prior history of nosebleeds except minor

nosebleeds as a child. A computed tomography scan at an outside hospital revealed a large pituitary mass, and the patient was transferred to our neurosurgical service for further evaluation. Endocrinology was consulted for evaluation of the pituitary mass.

### Past medical history

His medical history was only notable for asthma.

### Medications and allergies

Medications included albuterol as needed. There were no known drug allergies.

### Family history

There was no known pituitary or parathyroid disease.

### Social history

He was a high school student who lived with his parents.

### Review of Systems

The patient reported increased fatigue over the previous year. His weight was stable. He did not experience any visual symptoms but did report headaches as previously noted. He denied gynecomastia, galactorrhea, testicular atrophy, voice changes, or decreased libido. He shaved twice per week. There were no changes in the skin, hair, or nails. There was no increased sweating, foul smelling sweat, or excessive skin tags. He noted that he felt like his fingers were “getting stuck” but denies other joint pains. There were no symptoms of carpal tunnel syndrome, tarsal tunnel

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syndrome, or other nerve compression syndromes. He denied a history of light-headedness, dizziness, or fainting spells. He had always been thirsty but denied nocturia.

Of interest, the patient he felt he was still growing at the time of presentation. He wore a size 13 shoe, but he noted that he always had large feet. There was no change in his bite or changes in his facies. Growth curves from his pediatrician were obtained; the patient has deviated from the growth curve since he was 11 yr old. Until age 11, he was near the 50th percentile for height. By age of 15, he was at the 75th percentile. On presentation (at age 19), he was at approximately 94th percentile for age. The father is 5'8" and his mother is 5'5" (mid-parental height 5'9"). He reported "tall" uncles and a half brother. He was on the 50th percentile for weight until he was 5 yr old; at age 8, his weight was at the 90th percentile and has continued to remain at that percentile.

## Physical Examination

The patient was 6' 1.75" inches tall. He appeared to have coarsening of his facial features compared with a previous image on his driver's license obtained at age 16. The visual fields were grossly intact and the extraocular muscles were intact. No papilledema on fundoscopic exam. He had good dentition but did have an underbite that was most prominent on the right side of the jaw. The tongue was somewhat large. There was no thyromegaly or thyroid nodules. Heart was regular rate without murmurs, without gross cardiomegaly. The lungs were clear bilaterally. Abdomen exam was benign without organomegaly. The testicular exam was normal. There was no edema. There was no joint erythema or swelling. Tinel's sign was negative. There were no rashes or skin tags. The cranial nerves were intact and the neurological exam was normal.

## Laboratory data

The electrolytes revealed a sodium of 140, potassium 4.1, BUN 24, creatinine 0.7, and glucose 99. The WBC was 6.4, hematocrit 35.1, and platelets 256. The

PT and PTT were normal. Hormonal testing revealed that the FSH was 4.8 mIU/ml (1.5–12.4 mIU/ml for adult men), LH 3.7 mIU/ml (1.7–8.6 mIU/ml for adult men), testosterone 55 ng/dl (280–800 ng/dl), and PRL 247 ng/ml (4–20 ng/ml). The TSH was 0.93  $\mu$ IU/ml,  $T_3$  was 131 ng/dl (80–200 ng/dl), and  $FT_4$  level was 0.6 ng/dl (0.93–1.7 ng/dl). GH level was elevated at 30.8 ng/ml. IGF-I level was elevated at 828 ng/ml (182–780 for a 16- to 24-yr-old male). After 250  $\mu$ g iv cosyntropin, the cortisol values were 2.7  $\mu$ g/dl, 16.9  $\mu$ g/dl, and 19.3  $\mu$ g/dl at 0, 30, and 60 min. (The initial cortisol was suppressed because he briefly was on dexamethasone replacement when the cortisol stimulation test was administered.) After administration of 75 g oral glucose, the glucose was 87 mg/dl fasting, 93 mg/dl at 1 h, and 75 mg/dl at 2 h. The GH was 15.9 fasting, 14 at 1 h, and 15.6 at 2 h.

A pituitary magnetic resonance imaging (MRI) revealed an area of low signal which was indicative of pituitary macroadenoma following gadolinium. The pituitary gland measured 2.4  $\times$  2.3 cm in the transverse and superior inferior dimension. There was suprasellar extension with indentation on the optic chiasm. There was no evidence of cavernous sinus invasion or hemorrhage.

## Background for Discussion

Pituitary adenomas represent 10–15% of intracranial tumors. Historically, pituitary adenomas were classified according to their staining characteristics that included acidophilic, basophilic, and chromophobic tumors. Forms of pituitary adenomas include nonsecreting adenomas and those that secrete prolactin (PRL), GH, ACTH, or TSH.

The incidence of acromegaly is three to four cases per 1 million (1). It may have an insidious presentation and often remains undetected for up to 10 yr. It is characterized by hypersecretion of GH, which stimulates the hepatic production of IGF-I. The majority (>95%) of cases are caused by a pituitary adenoma. In addition to clinical manifestations arising from elevated GH and IGF-I levels, clinical manifestations include symptoms from local tumor growth such as headaches or visual field loss

and symptoms caused by decreased secretion of other pituitary hormones.

## Clinical Questions Raised in This Case Report

**1) The patient has both elevated PRL and GH levels. Does the tumor secrete both hormones or is the elevation in PRL secondary to a "stalk effect"?**

The normal range of PRL levels is 5–20 ng/ml. One can see values of 20–200 ng/ml for any sellar mass or for prolactinomas that are less than 1 cm. If a prolactinoma is 1–2 cm, PRL levels can be 200–1000 ng/ml. If a prolactinoma is greater than 2 cm, the PRL levels can be greater than 1000 ng/ml.

Of note, 30% of patients with acromegaly may have PRL-cosecreting tumors. However, one must carefully evaluate whether the adenoma is a PRL-GH *vs.* pure GH-secreting adenoma. Mild elevations in PRL can be associated with stalk compression. In addition, classification in the literature has been based on immunohistochemical staining, elevated serum PRL levels, or both methods. For instance, one study looked at 13 normoprolactinemic and 9 hyperprolactinemic subjects with acromegaly (2). Eleven adenomas had cells that stained for GH only, and 11 adenomas had a variable proportion of cells (10 to 98%), which also stained for PRL. In eight of the normoprolactinemic patients, there were no cells which contained PRL, and in five of the normoprolactinemic patients, 10–26% of cells positively stained for PRL. In the hyperprolactinemic patients, six patients had tumors that contained mammosomatotrophs (18–80%) and mammotrophs (0–18%). There was a positive correlation between PRL levels and the number of mammosomatotrophs.

**2) The patient significantly deviated from the growth curves and is taller than his midparental height. Could his tall height be due to excessive GH?**

Nonendocrine causes of overgrowth in children include familial tall stature, Klinefelter's syndrome, and Marfan's syndrome. Endocrine causes of overgrowth in children include precocious

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puberty, GH excess, and sex hormone deficiency or insensitivity.

A previous case report illustrates tall stature due to sex hormone insensitivity. The report described a 28-yr-old man who had estrogen resistance due to a mutation in the estrogen receptor gene (3). He had normal prepubertal growth and normal onset of secondary sexual characteristics. At age 16, the subject was 70" tall, and at age 28, the subject was 80.3" tall, with an armspan of 83.8" and a bone age of only 15 yr. The serum testosterone level was normal and the estradiol level was elevated. The findings indicated that androgens alone are not sufficient to promote skeletal maturation, and estrogen is important in bone development and mineralization in men.

GH excess in children can lead to gigantism, which is extremely rare. The open epiphyseal growth plates allow for excessive linear growth (4). A previous case report describes a 15-yr-old girl who presented headaches and fatigue and a large sellar mass was noted on MRI (5). She had a height increase of 3 in. during the previous year. After two surgeries, treatment with a long-acting somatostatin analog and a dopamine agonist controlled her biochemical parameters. Gigantism is quite rare, with only 100 cases described in the literature, although this may be an underestimate of the actual number of cases (4). Acromegaly and gigantism can be thought of as existing along a spectrum of GH excess. Ten percent of acromegalics have tall stature, and most subjects with gigantism exhibit clinical features of acromegaly.

### 3) What treatment options should be considered in this patient?

Treatment options include surgical treatment (translabial or transnasal), radiation therapy, or medical therapy. Medical treatment options include somatostatin analogs (octreotide or lanreotide), dopamine agonists, or a GH receptor antagonist (Pegvisomant). Two clinical trials that assess treatment options in acromegaly will be reviewed.

GH is a protein that contains 191 amino acids and is 22,000 Daltons (6). GH contains two distinct domains that bind to the GH receptor and produce receptor dimerization. Pegvisomant leads to non-functional dimerization of the GH receptor. Side effects of GH receptor antagonists include development of antibodies, injection site reaction, abnormal liver function tests, and a potential for increase in tumor size. One study evaluated the use of pegvisomant in the long-term treatment of acromegaly (7). In this study, 160 patients were treated with pegvisomant for an average of 425 d. The mean IGF-I levels decreased by 50%, whereas GH levels increased by 12.5 to 14.2 mg/liter. Progression in tumor size of the tumor was noted in two patients, although the cause of progression was unclear.

Dopamine agonists could also potentially be used for the treatment of acromegaly. In a prospective, open-label study of 64 patients with acromegaly treated with cabergoline, 39% of the subjects had IGF-I levels below 300  $\mu\text{g/ml}$  and 28% of the subjects had IGF-I levels from 300 to 450  $\mu\text{g/ml}$  (8). Of note, in the 16 subjects with GH/PRL cosecreting tumors, 50% of the subjects had IGF-I below 300  $\mu\text{g/ml}$  and 31% of the subjects had IGF-I from 300 to 450  $\mu\text{g/ml}$ .

### Conclusions

The patient was ultimately placed on thyroid replacement for his mild hypothyroidism and testosterone replacement therapy for the hypogonadism.

Repeat baseline laboratories were drawn in the patient—the IGF-I level was 850 ng/ml and the PRL was 208 ng/ml. He underwent a trial of medical therapy. The patient underwent a trial of cabergoline, which ultimately was titrated up to 1 mg three times/wk. After this trial, the IGF-I levels were 908 ng/ml, and the PRL level was 64.5 ng/ml. The patient subsequently underwent a trial of somatostatin, which was titrated up to 200  $\mu\text{g}$  three times/d. After this trial, the IGF-I level was 534 ng/ml, and the PRL level was 118 ng/ml. In

brief, there was little change in the IGF-I levels during these trials. Therefore, he underwent a transsphenoidal resection of the pituitary macroadenoma. The tumor reacted with antibodies to GH and PRL. It failed to react with antibodies to TSH, LH, FSH, or ACTH. One month postoperatively, he no longer experienced headaches. The IGF-I level was 541 ng/ml. The GH levels after 75 g oral glucose were 5.2 ng/ml at baseline, 4.4 ng/ml at 30 min, and 5.1 ng/ml at 60 min. Subsequently, he was started on pegvisomant due to persistently high GH and IGF-I levels. On therapy with pegvisomant, the PRL level improved to 14.5 ng/ml and the IGF-I level was 314 ng/ml. Postoperative MRI revealed a focal area of hypoenhancement in the sella, which measured  $1.4 \times 0.8$  cm and was mildly increased compared with a previous MRI where the area measured  $1.2 \times 0.7$  cm. A follow-up MRI will be obtained to assess for further changes in lesion size.

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## FOUNDATION NEWS

### EFF Announces Two New Research Grants for 2009

Generous support from two loyal supporters has been received by EFF, giving us the opportunity to offer two new research grant programs, in addition to our traditional grant.

#### 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 will be awarded at \$20,000.00 each. The object of this grant is to foster career development, and to that end this grant is potentially renewable for up to 3 yr, including post-fellowship research. A grantees fellowship program can progress to junior faculty utilizing the “young investigator award program” supported by this Amylin grant. Successful grantees will be required to present their research at an EFF scientific forum and publish abstracts of their research in *EndoTrends*.

#### Marilyn Fishman Grant for Diabetes Research

The second new research grant, named in honor of EFF’s long-time executive director, is funded through an unconditional educational grant from the partnership of Bristol-Myers Squibb and AstraZeneca International. This grant is limited to studies involving type 2 diabetes, and EFF plans to award up to ten research grants for \$15,000.00 each in 2009. Successful grantees will be expected to present their research at an EFF scientific diabetes forum for fellows and/or publish an abstract of their research in *EndoTrends*.

#### The EFF Endocrine Research Grant

Our traditional grant, the EFF grant in general endocrinology, is awarded twice a year and is for general endocrine topics including, but not limited to, thyroid, bone, adrenal, pituitary, growth, and reproductive disorders. Up to ten grants can be awarded in 2009 at \$7,500.00 each. Successful grantees will be expected to present their research at an EFF scientific endocrine-related forum for fellows and/or publish an abstract of their research in *EndoTrends*. The deadline for filing an application for Cycle 1, Spring 2009 was February 27, 2009. Cycle 2, Fall 2009 applications will be available early June 2009 and the application deadline will be August 10, 2009. Download these important grant applications from our web site, [www.endocrinefellows.org](http://www.endocrinefellows.org).

#### EFF Needs Your E-Mail Address!

EFF is moving into the electronic age and will be communicating with its constituents via e-mail in the future, delivering upcoming event and grant information faster and easier than snail mail.

In order to accomplish this, we have updated the EFF web site to include a new feature called myEFF. Using the myEFF feature will allow you to:

- Access and maintain your own personal information, letting us and your colleagues know when you move to a new institution or change your contact information.
- Update your profile.
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- Look for new services being added in the future.

If you are already in our database and we have your correct e-mail address, you can access your record now by using your e-mail address as your login

and Password1 (case sensitive) as your initial password. Once in the system, you can change the password to one of your choosing. If you are not in the database, or do not have an e-mail address on file, contact us at [info@endocrinefellows.org](mailto:info@endocrinefellows.org) and we will help you get started.

Don’t miss out on any new EFF information—check out the web site at [www.endocrinefellows.org](http://www.endocrinefellows.org) today and make sure we have your correct contact information. Especially that all important e-mail address!

### EFF Announces the 7th Annual EFF/ADA Endocrine Fellows Forum: June 4, 2009, New Orleans, Louisiana

EFF will be co-sponsoring the 7th Annual EFF/ADA Endocrine Fellows Forum in conjunction with the 69th Scientific Sessions of the American Diabetes Association on June 4, 2009. The forum will be held at the Ernest N. Morial Convention Center, New Orleans, LA, the day before the ADA meeting starts, and will provide endocrine Fellows an opportunity to gain a better understanding of today’s challenges in current management of diabetes from some of the world’s most acclaimed thought leaders.

On a first-come-first-served basis, Program Directors from around the country will be asked to nominate one Fellow from their program to attend this sponsored event. Air fare, hotel, and meals will be covered for up to 60 participants, allowing for an intimate and informal education experience, thanks to the generous support of unrestricted education grants from Merck & Co., Inc. and sanofi-aventis. The program details were mailed out in January 2009, and the deadline for registration was March 16th.



### Case Report

# Rapid Onset Diabetes or a Tipping Point? The Role of Antipsychotics in Type 2 Diabetes Mellitus

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New York, New York

## Summary

**Objective:** Diabetes mellitus (DM) and schizophrenia are being diagnosed at an all-time high. The unifying factor between these two conditions is the use of second generation antipsychotic medications. A case is described of a patient who developed rapid onset type 2 DM over a 4-wk period. **Methods:** The patient is a 25-yr-old male recently diagnosed with schizophrenia and started on antipsychotic medication. Before medication, the patient's body mass index (BMI) was 31 and fasting glucose was 103 mg/dl. The patient had no significant past medical or surgical history. Pertinent family history included DM in his mother, aunt, and sister. Four weeks after the initiation of antipsychotic medication, the patient had a blood glucose of 522 mg/dl with a BMI of 34.8. **Results:** After a few days the serum glucose was controlled with metformin 1000 mg twice daily, glargine 20 U at bedtime, and aspart 5 U before meals. **Conclusion:** Patients diagnosed with schizophrenia may have an increased risk for insulin resistance independent of exposure to antipsychotics. The use of second generation antipsychotics compounds this predisposition to develop type 2 DM. Certain second generation antipsychotics are associated with less insulin resistance, and these should be considered first line therapy. Insulin resistance secondary to antipsychotics occurs both with, and without, increases in adiposity. The use of metformin and exenatide in conjunction with the initiation of antipsychotic medication may prevent rapid onset type 2 DM in the psychiatric population.

## Introduction

Diabetes and schizophrenia are two major illnesses that challenge physicians, patients, and the health care system on a daily basis. With the recent increase in

obesity, the number of patients being diagnosed with diabetes is at an all-time high. Diabetes statistics from 1990–1998 demonstrate a 70% increase in the ages 30–39 population, 40% increase in the ages 40–49 population, and a 31% increase in the ages 50–59 population (1). In addition, mental illnesses like bipolar disorder and schizophrenia affect 57.7 million people ages 18 and older in the United States (2). In the midst of these numbers, there has become a unifying factor between these two conditions: the use of newer antipsychotic medications.

There is a positive correlation between the use of the newer antipsychotic medications and the development of type 2 DM in the psychiatric population (3). The etiology of this correlation involves increased adiposity, cellular changes in glucose regulation, or a combination of both. Increased adiposity is a known risk factor for decreases in insulin sensitivity and changes in both plasma glucose and lipid levels in patients treated with the newer antipsychotic medications (4). In essence it is this same increase in adiposity that is associated with the tremendous increase in type 2 DM during the last 10 yr. Recent reports have shown that the use of newer antipsychotic agents have led to rapid onset type 2 DM in antipsychotic naive patients, independent of weight gain, with a corresponding temporal relationship between drug initiation and the onset of hyperglycemia (5).

The mechanisms whereby type 2 DM is induced rapidly, as a medication side-effect, may compound the presence of the increased insulin resistance that already exists in many of these patients before the initiation of antipsychotic medication (6). It has been demonstrated that antipsychotic medications clearly affect glucose regulation inde-

pendent of adiposity, and several mechanisms have been proposed for these metabolic consequences (7). Some studies suggest that antipsychotic medications induce hyperglycemia via inhibition of peripheral glucose uptake (8), whereas others have demonstrated that expected  $\beta$ -cell compensation for insulin resistance may be reduced, or eliminated by, antipsychotic medications (9).

We describe a case of a patient who developed rapid onset type 2 DM over a 4-wk period. There was a temporal relationship between the initiation of antipsychotic treatment, substantial weight gain, and severe hyperglycemia. The purpose of presenting this case is to continue to heighten physician awareness of this issue, offer guidelines, and develop interventions based on new research to facilitate both mental and physical health in these patients.

## Case Report

The patient is a 25-yr-old male, recently diagnosed with schizophrenia, who was evaluated by the endocrine consult service for capillary blood glucose of 522 mg/dl. The patient was admitted to the psychiatric unit approximately 4 wk prior with an admission blood glucose level of 103 mg/dl, and he had been started on risperidone. However, due to side-effects of drooling, somnolence, and agitation, the patient was switched to olanzapine 2 wk later. He remained on olanzapine for the next 2 wk until he developed uncontrolled blood glucose.

On admission, the patient's weight was 89 kg, and his height was 167 cm (BMI = 31). He had no other significant past medical or surgical history, and he had not previously taken any antipsychotic medications. Pertinent family history included DM in his mother, aunt,

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### Blood Glucose Trend

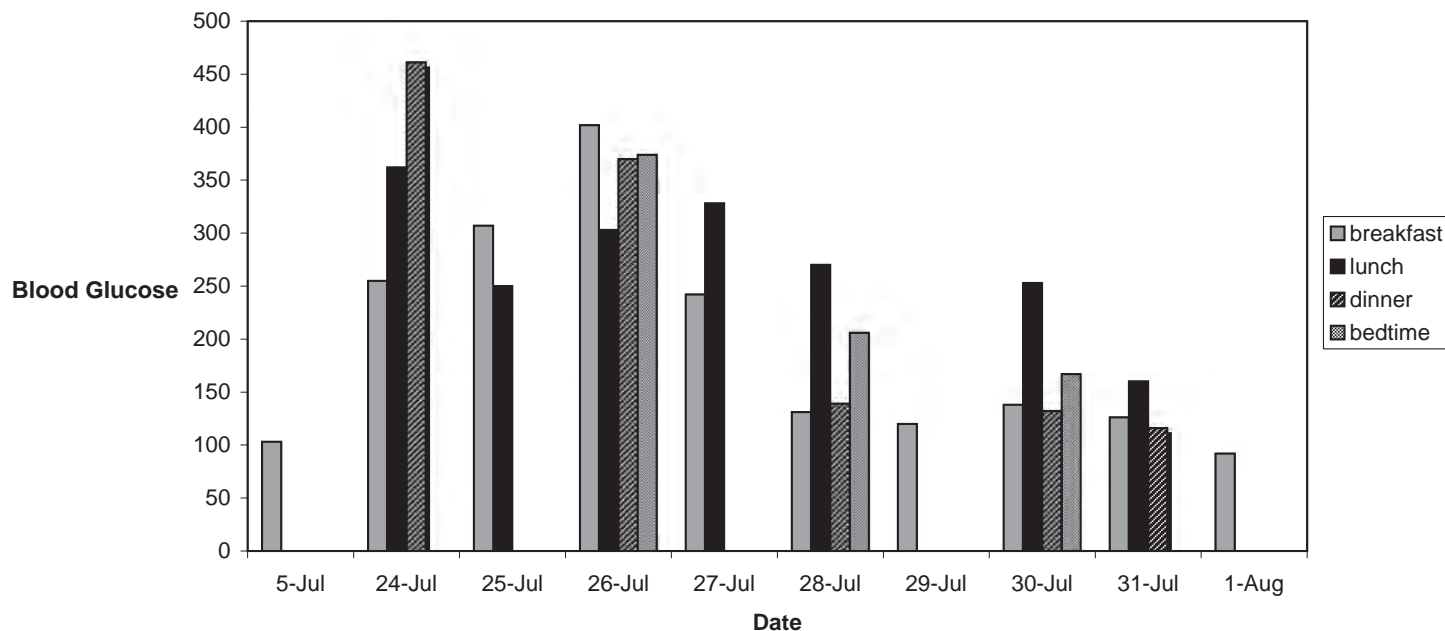


Figure 1. Serum blood glucose from d 1–9 of consult.

and sister. Social history included a few cigarettes per day with occasional alcohol and marijuana use. The patient had no known drug allergies. Review of systems included insatiable hunger, polydipsia, and polyuria. He denied headache and blurry vision. These symptoms were not noted before admission. Pertinent physical exam findings included a weight of 97 kg (BMI = 34.8).

Capillary blood glucose ranged from 462 on the morning of the consult to greater than 600 for the remainder of the day despite insulin coverage. Laboratory values did not reveal an anion gap, and a serum acetone level was negative. Hemoglobin A1C was found to be 8.9.

Olanzapine was stopped, and he was switched to perphenazine. The patient was started on glargine 20 U at bedtime and metformin 500 mg twice daily. The finger sticks remained elevated for a few days but were then controlled with metformin 1000 mg twice daily, glargine 20 U at bedtime, and aspart 5 U before meals (Fig. 1). The patient was discharged on metformin 1000 mg twice daily and glimepiride 4 mg daily. The patient did not require insulin at the time of discharge.

### Discussion

The advent of the newer antipsychotic medications was a revolutionary break-

through for the treatment of patients with schizophrenia. These agents provide effective treatment for both positive and negative symptoms while minimizing the extrapyramidal effects notorious in the older antipsychotic agents. However, an equally, if not more serious side-effect of these newer agents has been observed: insulin resistance. We report the case of a young man who developed severe hyperglycemia over a 4-wk period that corresponded with the initiation of antipsychotic medication.

Given the patient’s family history and unstable psychiatric presentation, the patient was at a high risk for the development of type 2 DM. Compared with the general population, life expectancy in patients with schizophrenia is shorter by as much as 20%; this is attributable to higher rates of suicide, accidental deaths, and death from natural causes such as cardiovascular disease, infectious disease, and endocrine disorders (10).

The guidelines concerning antipsychotics and obesity and diabetes recommend baseline screening measures, such as family history, weight and height, waist circumference, and fasting plasma glucose prior to, or as soon as clinically feasible, the initiation of antipsychotics (11). As an essential

follow-up to screening, there are further steps physicians can take to prevent the onset of diabetes in the psychiatric patients. Numerous studies since the publication of the most recent guidelines contribute valuable information to be utilized in this setting.

Patients diagnosed with schizophrenia may have increased risk for insulin resistance and type 2 DM independent of exposure to antipsychotics (12). Based on this knowledge, steps should be taken to control for this predisposition. Studies have indicated that certain antipsychotics, particularly olanzapine and clozapine, result in increased weight gain and insulin resistance when compared with other antipsychotics (13). Therefore, agents associated with less weight gain and insulin resistance, such as ziprasidone, risperidone, and aripiprazole, should be considered first line in these patients. The initiation of an agent less likely to cause weight gain would be a positive preventive step against the development of diabetes.

The weight gain in schizophrenic patients on antipsychotics goes beyond sedentary lifestyle and poor diet. Antipsychotics interact with various neurotransmitters involved in satiety, food intake, and glucose metabolism. For ex-

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ample, many antipsychotic medications bind to and block histamine receptors, and in the absence of antipsychotic medications it is the activation of these receptors in the hypothalamus that is associated with decreased food intake (14). Therefore, an agent that counteracts this effect would be beneficial in preventing excessive weight gain in this population. Studies investigating the use of exenatide in this setting may demonstrate that the medication's action on satiety and glucose-dependent secretion of insulin would produce favorable results when administered in conjunction with antipsychotics.

The diabetes prevention program demonstrated that, in patients with impaired fasting plasma glucose, the initiation of metformin 850 mg twice daily reduced the incidence of diabetes by 31% over 3 yr when compared with placebo (15). Because metformin is successfully utilized in this population after the development of type 2 diabetes to increase insulin sensitivity, further studies should investigate the use of metformin in conjunction with the initiation of antipsychotic medications. This would be similar to the common practice of using aspirin to relieve the side-effects of niacin or bupropion to relieve extrapyramidal side-effects from haldol.

The treatment of psychiatric illness poses a large challenge, and the use of psychotropic medication is a major tool. With the knowledge that the use of medications to fight one illness may predispose a patient to another illness, greater investigation is required. The patient presented in the current study may have been on course for diabetes despite the initiation of antipsychotics. However, awareness and early intervention for these patients can make a profound difference both physically and mentally.

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Bone, Fat and Brain Connections**

American Society for Bone and Mineral  
Research

*Bethesda, MD*

[www.asbmr.org](http://www.asbmr.org)

## MAY 2009

May 13–17

**18th Annual Meeting and Clinical  
Congress**

American Association of Clinical  
Endocrinologists

*Houston, TX*

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## JUNE 2009

June 4

**7th Annual Endocrine Fellows Forum**

Endocrine Fellows Foundation

*New Orleans, LA*

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June 5–9

**69th Scientific Sessions**

American Diabetes Association

*New Orleans, LA*

[www.diabetes.org](http://www.diabetes.org)

June 10–13

**51st Annual Meeting**

The Endocrine Society

*Washington, DC*

[www.endo-society.org](http://www.endo-society.org)

## SEPTEMBER 2009

September 11–15

**31st Annual Meeting**

American Society for Bone and Mineral  
Research

*Bethesda, MD*

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October 12–13

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