Case Study: Atypical Antipsychotic Use Associated With Severe Hyperglycemia

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Presentation
A.T. is a 50-year-old woman who developed acute hyperosmolar crisis. She first presented for primary care 5 months before the event. Medical history was notable for longstanding schizo-affective disorder and hyperlipidemia. She denied a history of diabetes. She reported her medication regimen had not changed in more than 1 year; medications included divalproex (Depakote), gabapentin (Neurontin), olanzapine (Zyprexa), and gemfibrozil (Lopid).

A.T.’s weight was 235 lb. A random plasma glucose was 103 mg/dl. Liver function tests, blood urea nitrogen, and creatinine were also normal. One month before the event, hydrochlorothiazide, 25 mg daily, was started for hypertension, and simvastatin (Zocor) was substituted for gemfibrozil to treat hypercholesterolemia.

One month later, A.T. presented to clinic with 1 day of urinary incontinence but no other symptoms of illness and was hospitalized for severe hyperglycemia. Her weight was 219 lb. Urinalysis showed no white blood cells but was strongly positive for glucose and weakly positive for ketones (trace). Her glucose level was 1,572 mg/dl, and her hemoglobin A1C (A1C) result was >14%. Her serum sodium was 113 mEq/l, potassium was 4.8 mEq/l, and carbon dioxide (bicarbonate) was 36 mEq/l. A.T. was severely volume-depleted as evidenced by postural hypotension, elevated blood urea nitrogen of 47 mg/dl, and elevated creatinine of 2.5 mg/dl. A semiquantitative blood acetone level was positive at a dilution of 1:8 (reference range is negative). A toxicology screen was negative. No evidence of infection, myocardial ischemia, or other acute illness was found. During the hospital stay, A.T. reported earlier treatment with glyburide (DiaBeta, Micronase, and Glynase) and metformin (Glucophage), but stated that those medications had been stopped more than 1 year ago for unknown reasons.

The patient was discharged from the hospital on a regimen of 14 units of NPH insulin with 14 units of regular insulin before breakfast, and 10 units of NPH insulin with 10 units of regular insulin before dinner. Olanzapine and hydrochlorothiazide were stopped, and haloperidol (Haldol) was started.

A few days after hospital discharge, A.T. presented to the clinic. She had skipped lunch, and her glucose was 48 mg/dl. Insulin was stopped.

Three months after stopping all hypoglycemic agents, she weighed 233 lb, her random glucose was 136 mg/dl, and her A1C was 7.5%.

About 4 months after hospital discharge, A.T. weighed 241 lb, and review of her glucose meter memory function showed random glucose levels were all >200 mg/dl. Her A1C was 10.3%. She was started on repaglinide (Prandin), and within a few months, a fixed dose of ultralente insulin was added.

Questions
1. Why did this patient develop severe hyperglycemia?
2. How is diabetes best managed in patients with severe psychiatric disorders?

Commentary
Hyperosmolar hyperglycemic nonketotic syndrome (HHNS) is defined as glucose >600 mg/dl and serum osmolality >320 mOsm/kg in the absence of significant ketoacidosis.1 Signs and symptoms include acute or subacute changes in mentation, temperature dysregulation (hyperthermia or hypothermia), relative hypotension, and renal insufficiency. The condition typically affects patients with type 2 diabetes who are over age 50. HHNS is often triggered by a physiological stress that causes hyperglycemia and dehydration, such as infection, myocardial infarction, stroke, or heat stroke. Medications associated with HHNS include glucocorticoids and diuretics. Recently, the newest generation of antipsychotic agents, referred to as “atypical antipsychotics,” have been associated with diabetes, severe hyperglycemia, and diabetic ketoacidosis.2

A.T. clearly met the criteria for HHNS, since her calculated serum osmolality was 340 mOsm/kg, using the formula: serum osmolality = 2(Na + K) + (blood urea nitrogen/2.8) + (glucose/18). She did not have obvious acute mental status changes, but subtle deficits may have been masked by her chronic psychosis.

Why she developed HHNS is less clear. It seems unlikely that low-dose hydrochlorothiazide alone triggered such severe hyperglycemia. Olanzapine, an atypical antipsychotic medication, was likely a major factor.

Atypical antipsychotics cause weight gain, and this is thought to be the primary reason that mild to moderate...
hyperglycemia is often associated with these medications.\textsuperscript{3} However, severe hyperglycemia that resolves with discontinuation of the medication has also been reported. The mechanism for acute, transient hyperglycemia remains unclear, although one study demonstrated that these medications inhibit glucose transport into cells.\textsuperscript{4}

Atypical antipsychotics offer many benefits over older antipsychotics, and they are now commonly used to treat many psychiatric conditions, including agitation in elderly patients with dementia. Patients who use these medications should be monitored for hyperglycemia. However, as this case demonstrates, severe, acute derangement of glucose control can occur even when a patient has been stable on medication for months to years.\textsuperscript{5}

This case also illustrates the challenges of treating diabetes in patients with severe psychiatric disorders. Members of a multidisciplinary psychiatric team see A.T. several times a week. Nevertheless, she has persistent problems with tangential thoughts, poor judgment, and delusions. Despite inpatient and outpatient diabetes education and frequent reinforcement from her medical providers, she has been unable to apply this knowledge in her daily life. For example, she can test her blood glucose and identify whether the result is low, acceptable, or high. When faced with a low blood glucose, she is able to state that consuming juice and a snack is advisable. However, she may then begin to focus on her desire to lose weight or her frustration with diabetes in general and decide not to follow any advice for treating the hypoglycemia.

Very little is written about managing diabetes in patients with severe psychiatric conditions. Ideally, such patients would live with a responsible person who helps manage their diabetes. For patients without a close friend or relative who is willing to assume this role, alternatives include a paid caretaker or assisted living.

However, poor judgment and lack of insight are inherent features of many psychiatric disorders. Therefore, some psychiatric patients will refuse help with diabetes management. State laws vary with regard to the involuntary confinement and treatment of psychiatric patients who are unable to care for themselves.

Concerns about a patient’s capacity for self-care should be discussed with the patient and the patient’s psychiatric team. If appropriate, judicial review of the patient’s situation should be considered.

### Clinical Pearls

- Atypical antipsychotics appear to increase the risk of type 2 diabetes by inducing weight gain. Less commonly, they have been associated with severe hyperglycemia that resolves or improves when the medication is stopped.
- Managing diabetes in patients with severe psychiatric disorders is especially challenging. Although diabetes education is important, not all patients will be capable of applying this information appropriately. The diabetes treatment plan should be realistic and account for the patient’s situation.
- Strategies to minimize the risks of treating diabetes in psychiatric patients include:
  - Enlisting the help of a caretaker whenever possible.
  - Treating mild hyperglycemia with medications only in carefully selected patients.

✔ Using oral agents and/or long-acting insulin to control severe chronic hyperglycemia.
✔ Before using metformin, determining whether the patient is likely to stop it if dehydration occurs.
✔ Before using short-acting insulin, determining whether the patient is likely to take it with food.
✔ Prescribing small quantities of insulin using prefilled syringes or insulin pens when appropriate.
✔ Encouraging patients to wear a medical alert bracelet or necklace that lists diabetes.

- In patients for whom tight glucose control is not realistic, other aspects of diabetes care may be especially important, such as treatment of hypertension and hyperlipidemia; regular screening for retinopathy, neuropathy, and nephropathy; and aspirin therapy.

### REFERENCES

Case Study: Necrotizing Fasciitis in a Patient With Obesity and Poorly Controlled Type 2 Diabetes

Anca M. Avram, MD

Presentation

E.N. is a 60-year-old white woman who presented at the hospital with high fever, chills, and severe pain at the base of her neck. She was unable to flex or rotate her neck because of pain and swelling. She recalled that 3 days before admission, there was an unusually warm winter day, and she walked in a nearby park enjoying the weather. She recalled an itching and painful sensation that she initially attributed to a spider/insect bite on her upper back, which gradually progressed to severe pain and swelling over the next 2 days.

Her medical history was significant for type 2 diabetes for the past 5 years, class 2 obesity (body mass index 37.5 kg/m²), and hypertension for the past 10 years. Her medications were glyburide (Micronase), 5 mg twice daily, and verapamil (Calan SR), 240 mg daily. She did not smoke or drink alcohol. Her family history was significant for mother with type 2 diabetes and hypertension.

At admission, E.N. was febrile (temperature 40°C), tachypneic (respiratory rate 20), tachycardic (heart rate 120), and hypertensive (blood pressure 164/69 mmHg). Physical examination revealed a large area of wood-like induration (5 × 6 inches) extending from the back of the neck forward to the chin and downward to the upper back. The skin was darkly erythematous, and there was a central area of excoriation with yellow crust. Admission laboratory studies revealed hemoglobin 13.7 g/dl, white blood count 13.6 K/mm³, bands 10%, plasma glucose 356 mg/dl, and hemoglobin A₁c 10.2%. Blood cultures were performed, and the patient was treated with high-dose intravenous antibiotics.

Questions

1. What is the diagnosis?
2. How should this patient be managed?
3. What are the microorganisms producing this fulminating infection?
4. How is the patient predisposed to developing this condition?

Commentary

E.N. underwent computed tomography (CT) imaging of the neck and chest, which showed extensive gas formation in the soft tissues of the right back neck dissecting along the fascial planes toward the front neck and upper back. Based on clinical presentation and CT images (Figures 1 and 2), E.N. was diagnosed with necrotizing fasciitis.

CT diagnostic criteria for necrotizing fasciitis are asymmetric fascial thickening associated with fat stranding and gas tracking along the fascial planes. In advanced cases, the infection can extend to the adjacent muscles, with gas present within the muscle mass characteristic of myonecrosis. Imaging modalities detecting the presence of gas in the soft tissues are plain radiography of the involved areas, ultrasonography of the subcutaneous tissue in the case of Fournier’s gangrene, CT imaging, and magnetic resonance imaging. CT imaging has the advantage of being readily available and offering an excellent depiction of the extent of soft tissue necrosis and of possible coexisting deep abdominal or pelvic abscesses.

With the diagnosis established, E.N. was immediately taken to the operating room for incision and debridement. Necrotizing fasciitis is a surgical emergency because the infection can spread in the subcutaneous tissue over a period of hours. Frequently, the severity and the extent of the infection are not initially appreciated. Delay in accurate diagnosis is associated with poor prognosis.

In E.N.’s case, surgery revealed extensive soft tissue necrosis of the cervical fascia extending to the carotid sheath, with involvement of the right trapezius and right sternocleidomastoid muscle. There was a large quantity of necrotic, foul-smelling tissue and thin, watery, brown discharge (classically described as “dishwater pus”). Gram stain of necrotic tissue specimens showed a polymicrobial bacterial population (many Gram-positive and Gram-negative cocci and many Gram-negative bacilli), and the culture identified staphylococcus epidermidis, streptococcus viridans, bacteroides ureolyticus, pseudomonas aeruginosa, proteus mirabilis, and enterococcus faecalis.

E.N. underwent multiple surgical debridements and was treated with large doses of intravenous antibiotics: clindamycin (Cleocin), 900 mg every 8 hours, and gentamicin (Garamycin), 450 mg every 24 hours. Blood cultures were repeatedly negative. Despite aggressive surgical and medical management, the patient developed septic shock and cardiopulmonary arrest, unresponsive to resuscitation attempts.

This case illustrates the evolution of necrotizing fasciitis, which is a deep and devastating soft tissue infection. In 80% of cases, the infection develops as an extension from a skin lesion (i.e., minor abrasion, insect bite, or injection site), but in 20% of cases, there is no visible skin lesion. The etiology can be monomicrobial (i.e., group A β-hemolytic streptococcus pyogenes, staphylococ-
necrotizing fasciitis by the tissue hypoxia caused by arteriosclerosis and the immunodeficiency associated with poor glycemic control. Neutrophil chemotaxis, adherence, phagocytosis, and intracellular oxidative killing have been shown to be defective in diabetes.

The pathological hallmark of necrotizing fasciitis is thrombosis of subcutaneous arteries and arterioles leading to extensive soft tissue necrosis. Early and aggressive surgical debridement of all involved tissues, combined with combination intravenous antibiotic therapy with broad spectrum coverage, is the cornerstone of therapy.

Early diagnosis based on clinical presentation and imaging modalities is essential in initiating medical and surgical treatment. In the absence of rapid control of the spread of the infection, necrotizing fasciitis progresses to disseminated vascular coagulation, septic shock, and death (cumulative mortality rate 34%).

Clinical Pearls

- Necrotizing fasciitis is a severe soft tissue infection occurring in patients with diabetes, morbid obesity, alcoholism, advanced atherosclerotic disease, and decubitus ulcers.
- Early diagnosis is essential for patients’ survival.
- CT imaging is very useful in identifying the presence of gas in soft tissues and gas tracking along the fascial planes.
- Aggressive surgical debridement and combination, broad-spectrum coverage intravenous antibiotic therapy are the cornerstones of therapy.

SUGGESTED READINGS


Anca M. Avram, MD, is a fellow in the Division of Endocrinology and Metabolism at the University of Michigan in Ann Arbor.
Case Study: A Woman With Type 2 Diabetes and Severe Hypertriglyceridemia Sensitive to Fat Restriction

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Presentation
L.S. is a 52-year-old Caucasian woman who was diagnosed with type 2 diabetes in 1988. She developed hypertriglyceridemia 3 years later and hypertension 9 years later. Other medical problems include obesity and diverticulosis. She presents now for screening to determine eligibility for a clinical research protocol using once-daily insulin.

Physical exam reveals a height of 64 inches, a weight of 181 lb, a body mass index of 31 kg/m², and a waist circumference of 40 inches. Blood pressure, well controlled on 20 mg lisinopril (Prinivil) daily, is 104/70 mmHg.

Laboratory results reveal a fasting lipid panel as follows: total cholesterol 214 mg/dl, triglycerides 940 mg/dl, direct HDL cholesterol 24 mg/dl, an invalid LDL cholesterol unobtainable because of the hypertriglyceridemia, and a free fatty acid of 1.1 mEq/l (normal range 0.1–0.6 mEq/l). Hemoglobin A₁c (A₁C) is 9.5%, and fasting blood glucose (FBG) is 304 mg/dl. When called to discuss the finding of severe hypertriglyceridemia, the patient commented that she had previously had fasting triglycerides as high as 3,000 mg/dl.

L.S. is currently taking metformin (Glucophage), 1,000 mg twice daily, and glipizide (Glucatrol XL), 10 mg twice daily, to control her blood glucose. She is also on gemfibrozil (Lopid), 600 mg twice daily, for hypertriglyceridemia and estradiol (Estraderm) for menopause (topical estrogen does not induce hypertriglyceridemia).

Questions
1. What nutritional modification would be effective in rapidly lowering serum triglycerides when the patient is at risk of pancreatitis?
2. What treatment strategies can be employed to lower triglycerides, and how effective are they?
3. How can nutritional modifications improve insulin resistance?

Discussion
Type 2 diabetes carries a two- to four-fold excess risk of coronary heart disease. The most common pattern of dyslipidemia in patients with type 2 diabetes is elevated triglycerides and decreased HDL levels. Although coexistent increases in small, dense LDL cholesterol particles—not the triglycerides themselves—may be responsible for the increase in cardiovascular risk, hypertriglyceridemia poses a significant burden on society.

In type 2 diabetes, characterized by insulin resistance and insulin deficiency, the pathophysiology of hypertriglyceridemia is an increased hepatic production of triglycerides as well as a decreased lipoprotein lipase activity leading to slower breakdown of VLDL cholesterol and chylomicrons. The American Diabetes Association (ADA) Clinical Practice Recommendations list serum triglycerides ≥400 mg/dl and an HDL level <45 mg/dl for women as indicative of high risk of coronary heart disease.

By both ADA and National Cholesterol Education Program (NCEP III) guidelines, the first goal for this patient is to lower triglycerides to prevent pancreatitis, which not only can result in hospitalization, but also is potentially lethal. Although L.S. is already on the maximum dose of gemfibrozil, her triglycerides are still inadequately controlled.

With triglycerides in this range, she should be alerted immediately to the fact that any alcohol, even that found in over-the-counter cold remedies can trigger pancreatitis until her serum triglycerides are brought down to a safer range (<500 mg/dl). In addition, a single high-fat meal can also trigger pancreatitis.

A severely restricted fat intake (<10% of daily kcal) can effectively bring down serum triglycerides by 20% per day until triglycerides are <500 mg/dl. A diet in which fat is so severely restricted usually brings about weight loss as well. A loss of 2.5 kg body weight would bring an expected 15–20% decrease in serum triglycerides. In addition, aerobic exercise can help to lower serum triglycerides by 10–15%.

Interventions to further decrease serum triglycerides to <200 mg/dl, increase HDL to 45 mg/dl, and decrease LDL to <100 mg/dl should be attempted to decrease the risk of coronary heart disease.

At the first clinic visit, L.S. was advised of the risk of pancreatitis and advised to forego any alcohol and to adhere to severe fat restriction until she has a fasting serum triglyceride level...
<400 mg/dl. She and her husband are both from the South, and their traditional Southern fare used quite a bit of salt pork, which deleteriously augmented the saturated as well as total fat in her diet. She had been advised to “watch her weight” when her triglycerides were in the 3,000 mg/dl range, but she had been unable to follow that recommendation.

Between clinic visits, L.S. was given written information about a low-fat (10% of kcal) diet, including lists of foods to restrict and foods to encourage until a more thorough meal plan could be developed based on an assessment of her previous dietary patterns. She was advised that this was a short-term, severe dietary change. She had already instituted an exercise program, walking for 1 hour, five times a week regularly.

Two weeks later, when L.S. returned to clinic after following the suggested fat restriction, her lab results showed the following lipid profile: serum total cholesterol 193 mg/dl, serum triglycerides 355 mg/dl, direct HDL cholesterol 32 mg/dl, and LDL cholesterol 90 mg/dl. Her A1C had dropped to 8.8% with no change in therapy for her diabetes, and her FBG was 158 mg/dl. Her fasting free fatty acid level was 0.7 mEq/l. Her weight had dropped by 3 lb.

At this visit, medical nutrition therapy (MNT) was initiated, and the patient was put on 10 units of 75/25 insulin before dinner.

Six weeks later, her A1C had dropped further, to 7%, her FBG was 110 mg/dl, and her weight was down another 2 lb. Her lipid profile was as follows: total cholesterol 181 mg/dl, triglycerides 299 mg/dl, direct HDL cholesterol 32 mg/dl, and LDL cholesterol 89 mg/dl. Her fasting free fatty acid level was now 0.6 mEq/l, the upper level of normal. Meal plan records showed that she was consuming ~1,500 kcal/day and getting ~25% of daily kcal from fat.

Commonly, controlling hyperglycemia leads to a decrease in triglycerides. However, in this patient, the clearing of serum triglycerides, the restricted saturated fat, and the weight loss had a substantial impact on improving glucose tolerance without adding further diabetes oral agents. Studies have shown that dietary fat, primarily saturated fat, has adverse effects on insulin sensitivity. Restricting fat intake, especially saturated fat, resulted in a better metabolic profile in regard to both glucose tolerance and fasting serum triglycerides.

Lifestyle changes had been recommended previously; why was L.S. successful this time when she hadn’t been before? The patient offered the following comments when asked this question.

- “I was handed written information, but concern about the numbers (hyptertiglyceridemia) was never conveyed.”
- “They tell you what you need to do, but not how or why to do it.”
- “No one sat down and talked with me. I never received individualized attention.”
- “If my triglycerides were potentially harmful, why did they not see me sooner than 3 months? Three months was the usual time between visits and again they conveyed no concern.”

In previous attempts to encourage this patient make lifestyle changes, the compliance approach was used, but the benefits of self-care, the costs of not complying, the susceptibility to pancreatitis and cardiovascular disease, and the severity of such elevated triglycerides were not conveyed. A referral to an educator, time spent in assessing eating patterns and teaching alternatives, and more frequent visits or follow-up serve to convey the importance of recommended lifestyle changes. MNT coupled with an empowerment approach through which patients are the primary decision makers is important.

Although lifestyle changes are always recommended as first-line therapy, the approach to helping patients achieve these lifestyle changes in busy office practices is too often insufficient. A new Medicare benefit effective January 2002 allows patients with diabetes access to insurance coverage for MNT. Evidence-based research shows that MNT provided by a registered dietitian experienced in the management of diabetes is clinically effective.

Clinical Pearls

- Reducing dietary fat improves body weight, which in turn improves glucose tolerance and hypertriglyceridemia.
- There is evidence that saturated fat may elevate plasma glucose by way of increasing insulin resistance.
- MNT for hypertriglyceridemia may be divided into three parts:
  1. When fasting triglycerides are ≥1,000 mg/dl, restrict dietary fat to 10% of kcal until fasting triglycerides fall to <500 mg/dl.
  2. For fasting triglycerides between 1,000 and 500 mg/dl, a) reduce saturated fat to <7% of energy and dietary cholesterol to 200 mg/day; b) increase viscous (soluble) fiber to 10–25 mg/day; c) encourage modest weight loss (5–7% of body weight); and d) increase physical activity.
  3. For fasting triglycerides <500 mg/dl, encourage weight loss and a decrease in simple sugars in addition to the above reduction in saturated fat.

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