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Cushing Disease: Diagnostic Pearls and Pitfalls CME / ABIM MOC / CE

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Posted: 12/16/2020

Educational Impact Challenge

Clinician Handout

The goal of this activity is to improve the recognition and diagnosis of Cushing disease (CD).

Before you begin this activity, please assess your clinical knowledge by completing this brief survey. Answering these questions again after the activity will allow you to see what you learned and to compare your answers with those of your peers.

Educational Impact Challenge

What did you learn from this activity? Please click on the "Next" button to proceed to a brief survey to see how your knowledge improved after the education. You can also see how your answers compare with those of your peers.

Educational Impact Challenge

A1c = glycated hemoglobin
ACTH = adrenocorticotropic hormone
BMI = body mass index
CD = Cushing disease
COVID-19 = coronavirus disease 2019
CRH = corticotropin releasing hormone
CS = Cushing syndrome
Dep = dependent
ER = emergency room
GH = growth hormone
GP = general practitioner
HCP = healthcare provider
Indep = independent
IQR = interquartile range
LNSC = late-night salivary cortisol
Ob/Gyn = obstetrician/gynecologist
PCOS = polycystic ovary syndrome
PCP = primary care provider
SD = standard deviation
SMR = standard mortality ratio
TE = thromboembolic event
UFC = urine free cortisol
VTE = venous thromboembolism

Activity Transcript

Beverly MK Biller, MD: Welcome to "Cushing Disease: Diagnostic Pearls and Pitfalls." It is such a pleasure for me today to introduce 2 friends and colleagues.

First, Dr Richard Auchus. He's the James Shayman and Andrea Kevrick professor of translational medicine at the University of Michigan. I would consider him one of the foremost adrenal physiology experts in the world. Next, we have Dr Maria Fleseriu, professor of medicine and also neurological surgery. She's in the division of endocrinology, diabetes, and clinical nutrition at the Oregon Health and Science University in Portland, Oregon. Maria is an expert in all things pituitary. I'm very excited that they're here with me today as we discuss the following topics.

We are going to address current gaps in the recognition and diagnosis of patients with Cushing disease. Next, we will discuss the clinical presentation of patients with this disorder. Finally, we'll finish up by discussing when we suggest referring patients, either from primary care providers, as some of you are, to an endocrinologist, or from an endocrinologist to a pituitary tumor center of excellence.

I want to start by just reminding all of us about the physiology of the hypothalamic pituitary adrenal axis. Since I know this is an audience with a broad group of physician specialties, we will start with a reminder that the hypothalamus in the brain produces corticotropin releasing hormone that travels down the pituitary stalk to trigger production of corticotropin or adrenocorticotropic hormone, which we abbreviate to ACTH. ACTH in turn travels through the body and passes through the adrenal glands where it triggers production of cortisol in pulses and with a diurnal pattern. We know that when the system is overactive, that produces Cushing syndrome. Of course, when it's underactive, that's hypoadrenalism or adrenal insufficiency. Today we're talking about Cushing, so let's do a few definitions of the terminology that can sometimes be confusing.

Cushing syndrome refers simply to all of the clinical features of excess cortisol, the conditions that it produces throughout the body, which you'll be hearing about it from my colleagues shortly. The most common cause of Cushing syndrome is us, that is we prescribe steroids for a long list of conditions. Iatrogenic Cushing, doctor-caused Cushing, is actually the most common, that is exogenous Cushing from outside the body. Today we are focused on talking about endogenous Cushing, cortisol excess from a tumor within the body that is either over-producing ACTH, and that in turn stimulates the adrenals, or directly producing cortisol.

If the problem is too much ACTH, we call that ACTH-dependent Cushing, and the most common cause of endogenous Cushing is from a pituitary tumor that is over-producing ACTH and that accounts from anywhere from about two-third to 80% of cases. It could also be from part of the body such as a lung tumor that acts like a pituitary gland, and overproduces ACTH, known as ectopic Cushing. Finally, the adrenal gland itself may develop a tumor which produces cortisol directly. Because this is not dependent on ACTH excess, that is termed ACTH-independent Cushing. When we say Cushing disease, as opposed to syndrome, we are referring specifically to a pituitary source of ACTH excess.

One of the interesting things to think about in the challenge of making the diagnosis, which you will hear a lot about shortly from Dr Fleseriu, is that there's not a standard common pathway of symptoms or signs through which a patient would present. As a result of that, the diagnosis is made by a wide range of different clinicians.

We had the opportunity to collaborate with the Cushing Support and Research Foundation, a patient support group, who surveyed their patients to ask who is the first person who suggested to you that you might have Cushing, and as you would expect most commonly, it is a physician, but in a surprising number of cases, it was either the patient or family members who suggested that they might be evaluated for this condition.

The most common type of physician who makes the diagnosis of Cushing is primary care providers and general practitioners. The next most common is endocrinology, but it is important to note that the front lines, primary care providers, are the people who most commonly move to the correct diagnosis and then subsequently refer the patient. It's also interesting to note that nurses, hospitalists, and a whole host of other specialties also consider this diagnosis if they recognize that some of the patient's features might be due to cortisol excess. When we are faced with a patient who might have Cushing, there are 3 logical steps to take in evaluating them. The first is to answer the question, does this person have endogenous Cushing syndrome or pathologic cortisol excess?

If the answer is yes, and only if the answer is yes, then we move on to looking for where in the body it might be, in the pituitary, in the lungs, or some other body part or the adrenal glands. The reason that's so important is that treatment depends on the location because we often start first with surgery. Now I'd like to turn things over to Dr Fleseriu who will tell you more about the condition of Cushing disease and making the diagnosis. Maria.

Maria Fleseriu, MD, FACE: Thank you, Beverly, it's a pleasure to be here and let's see where we are now.

In the diagnosis of Cushing in general, incidence is somewhere between 0.7 and 2.4, some studies are saying even 5/million people/year. How many are ACTH-dependent? Probably about 80%. This is Cushing disease and some other causes such as ectopic, as you heard earlier. The median age of onset diagnosis is around 40 years. What everybody agrees is that Cushing in general is significantly more frequent in female to male ratio, it's about 3:1. The rareness of the disease, the broad symptomatology without the lead symptom per se, and the clinical overlap with features of metabolic syndrome, as you'll hear later from Rich, often results in a delayed diagnosis.

Generally it can take up to 4 years and even longer from the beginning of disease symptoms to the actual diagnosis. On average, as you heard earlier, we don't even know sometimes who's making the diagnosis, but most of the patients are seeing more than 4 physicians. In a most recent systematic meta-analysis of 45 studies, over 5000 patients with Cushing syndrome, show that the time to diagnosis remained unchanged, and the mean time was 34 months in that particular meta-analysis. I would like to ask my colleagues if they agree with this data in their particular centers, and also what's the longest and the shortest time they have seen for a patient to be diagnosed after the onset of symptoms?

Richard Auchus, MD: We see the whole spectrum, depending on the type of disease. We have people with ectopic ACTH syndrome who very rapidly progress over a month or 2 to a critical state. We also have people that smolder for almost 10 years before they're diagnosed. Adrenal Cushing can be very, very slow in onset and very mild. So people present first with hypertension, then a couple years later with diabetes, then they're found to have osteoporosis and then you make the diagnosis after 10 or 15 years. I would say about 15 years is the maximum, but it's highly variable depending on the type of Cushing and the severity of it.

Dr Biller: I agree. Maria, one of the things you said that I completely agree with in terms of our experience is that many patients by the time they reach us have seen a number of other doctors. You mentioned the data that typically people have seen 4 to 5 doctors, and I think that's not at all an underestimate. It could be higher in many cases because they get referred for specific symptoms. They might have, for example, easy bruising, so they'll be referred to a hematologist, or they might have osteoporosis at an early age and broken bones, so they might see an orthopedist. They've kind of gone from doctor to doctor and it really takes someone putting it all together, which can take a while before they get the diagnosis of Cushing.

Dr Fleseriu: I agree. The reason the delay of diagnosis is so important is the fact that chronic exposure to cortisol excess leads to significant morbidity, especially in Cushing disease when the diagnosis is late.

We know that if the patients are not treated, the mortality is very high, up to 5.5-fold, with increased morbidity and definitely impaired health-related quality of life. The range of comorbidities is varying from osteoporotic fractures, diabetes, hyperlipidemia, opportunistic infection, and cardiovascular complications are still very severe from hypercoagulability, that we'll talk a little bit later about that, coronary heart disease, heart failure, cerebrovascular events, all these complications have to be monitored and adjunctive treatment needs to be done in addition to the treatment for Cushing itself. Why is this so important? It's that we know that if the duration of Cushing was very long, that would impact the severity and the extent of comorbidities, but also how reversible they are, and the mortality increases over time. For thinking about Cushing in general, this is one of the unmet needs, what to do about complications and how to best monitor for that. I'm curious what my colleagues are doing overall. Also, we still don't know, we're not going to talk about treatment per se, but after initial treatment, we still don't all agree how it's best to assess for admission for surgery. And, furthermore, how to look for when the disease is coming back, and then the goal of multidisciplinary treatment in center of excellence that we'll cover later, it's still a clear unmet need. But if we're talking about complications overall, the largest database, too, is coming from Europe**,** more than 1500 patients that were followed for more than 2.7 years and more than 1000 patients had Cushing disease showed that the mortality overall was 3.1, with 2.2 for Cushing disease. But what was very interesting is that 45% of that occurred within 90 days from start of treatment, and furthermore 10% of that were before even the treatment was given. Out of all these deaths, the infections were the most common cause of death at 37% and then progression of underlying tumor, 26%, all the way to diagnosis and active disease predicted long-term mortality. If we're looking into the most frequent complication that was not very well known before, and we still don't know how to prevent, a study retrospectively done in over 200 patients recently showed that about 20% of the patients have complications related to thromboembolic events, both arterial and venous. Interestingly 43.7 had these events at the time of the bilateral adrenalectomy and no other predicting factors were identified.

Overall looking at meta-analysis in general, we know now that more than 3% of Cushing patients experience venous thromboembolism and the odds ratio of these events are almost 18% compared to general population. We definitely need to do more in preventing these events. I would like to hear from my colleagues, how they approach these complications, when they will actually start thinking about treatment and anticoagulating, especially with a complicated relationship tree.

Dr Biller: It's certainly a hot topic, and I don't think anyone has the answer. What we've done in terms of anticoagulation really depends on the circumstance. For example, if it's the really sick type of patients with ectopic Cushing that Rich was mentioning, they would be anticoagulated if considered safe by their oncologist, because they're at very high risk, even from their tumor often. If it's a patient with the pituitary Cushing, the focus of today, our patients usually go to surgery within a week or 2 of the diagnosis being made and they spend between 24 and 36 hours in the hospital after the surgery. They are up and walking around within about 6 to 8 hours of the operation and if they are ambulatory, they are not given anticoagulation, but if they have complications or they're bedridden or going to stay in the hospital more than the usual day, then they would be treated with enoxaparin until they're fully ambulatory. How about you, Rich, what do you do?

Dr Auchus: Yes, similar. We have a very low threshold for anticoagulating after surgery. We tend not to anticoagulate before surgery. Somebody with adrenal Cushing, who's having an adrenalectomy, leaving the hospital the next day, mild Cushing, we probably wouldn't anticoagulate them at all. The ectopics, for sure. The pituitaries, our neurosurgeon has gotten more aggressive about anticoagulating them. Most of those patients will get anti-coagulated with low molecular weight heparin for a month post operatively.

Dr Fleseriu: That's very interesting. And our approach is about the same. Looking back at the data show that some of the patients had events despite anticoagulation, so I don't think we're going to find that answer very soon. Talking about registries, the most recent nation registry that's coming from Sweden looked at more than 500 patients with Cushing disease. Large majority, 77% were men, 83% were confirmed to be in remission. The mean age of diagnosis confirmed what we said earlier, around 43. It was long follow-up after 23 years with a median of 13 years. This study has been published recently so this is recent data that the standard mortality ratio was 2.5. Still very high, even in this era with multi-modal treatment, and the most common cause of death was cardiovascular disease, infections, and suicide. Furthermore, what's very important is the standard mortality ratio for patients who were in remission, so controlled Cushing, was 1.9.

Bilateral adrenalectomy and the glucocorticoid replacement therapies were independently associated with increased mortality. And we can talk definitely about that and how much we're probably over replacing patients, whereas growth hormone replacement was associated with improved outcomes. That study also showed that stroke, thromboembolism, and sepsis, though, were seen before the surgery and the diagnosis itself persisted for a year. Even in long term remission, all of these were much higher than normal population. And switching to how to assess risk of recurrence right now, another very interesting topic that we don't have a final answer, is different centers have different protocols. In general, we used to consider, if you'd have asked me several years ago, I would say that if the patient has adrenal insufficiency post-surgery their likelihood of recurrence is low. That shows that it's partially true, but everybody can recur. If the values are between 1.8 and 5 immediately after surgery suggest remission, but we can see recurrence much more frequently and definitely patients with cortisol postoperative more than 5 probably are not in remission.

We have seen patients that recurred significantly later that we used to think so right now I'm telling all the patients that you are in remission right now; you will need follow up for all your life because you might recur. I would like to hear from my colleagues, how do they monitor their patients with Cushing disease after pituitary surgery and what is the most delayed recurrence that they have seen, and which is their preferred test, if they have one?

Dr Auchus: Right. We measure cortisol and ACTH every 6 hours after the operation. We do not give them hydrocortisone until we document that the cortisol is less than 3, preferably on 2 successive labs, and then we start treatment and we confirm that the ACTH corresponding to that low cortisol is less than 10. Then after people are weaned off of hydrocortisone, we get late night salivary cortisols at 6 months, a year, and then once a year. The longest recurrence that I've seen was a person who in childhood had Cushing at age 12 and then had a recurrence at age 30.

Dr Biller: I'm really happy that you brought up recurrences, Maria, because I think that this is one of the unrecognized problems. We ourselves, I agree, did not recognize it for many years, but now we're seeing more and more patients who were placed in remission, even had those very, very low postoperative cortisol levels and were adrenally insufficient for a year, they're coming back and recurring. I'm not quite sure I can top Rich, but I'm pretty close. We've seen plenty of patients who've recurred at 5, 10, 15 years. The longest I've seen is a patient in recurrent at 21 years.

In fact it was. I think a really key message is what you said, Maria, that these patients need to understand that even when we can celebrate with them when they're in remission, from whichever treatment they've gotten, whether it's surgery or later medical or radiation treatment, they need to continue follow up for the rest of their lives.

Dr Auchus: I like to make 1 more point, which is that, unlike the diagnosis initially where they flounder for years, the patients usually know when they're having a recurrence, because they know how they felt when they had Cushing and they know it's coming back.

Dr Fleseriu: I agree. Which is your favorite test? None of you have answered that yet, to test for it.

Dr Biller: My favorite test would be late night salivary cortisol. We know from data in France that the late-night salivary test in people later proven to have recurred is the first test to become abnormal in most patients. It can take many months or even a year longer before the 1 mg overnight dexamethasone test becomes abnormal and later still for the urine free cortisols to become abnormal. I think Rich mentioned that he does them regularly, and we do as well, late night salivary cortisols, but I echo what you both said. The patient often knows before we can prove it biochemically. We now take it very seriously if the patient says to us, "I think it's back."

Dr Fleseriu: Definitely. We should tell all the patients much earlier that they should think about recurrence for all these symptoms.

Dr Auchus: The first point I want to make is that you will never make a diagnosis of Cushing syndrome if you don't suspect and screen patients. You're going to have to get some normal labs in order to make the diagnosis. The common features of Cushing syndrome lack specificity. Those are the obesity, the weight gain, glucose intolerance, hypertension, poor sleep, depression, irregular menses, and hirsutism. You probably each have dozens in your clinic with those features. Who do you test? I will get into some more specific features, but I guess I want to first ask Beverly and then Maria, what tips you off? What are your pearls of who do you need to think a little deeper in people presenting? Let's say they have some of these features that we talked about, but what else do you look for? What else do you ask them?

Dr Biller: Thanks, Rich. Two quick pearls. One is I look for a pattern of change over time. If someone has always had obesity and had acne, that's different in my mind from someone who didn't have those troubles and then over the last short amount of time started developing them. The second quick thing is I like to ask patients for their old pictures to see whether that also reveals a change over time. The last thing I'll

mention, which I suspect you may plan to talk about, is whether there are some of the more specific features, particularly proximal myopathy. I like to see if people can stand up from a stool that's low on the floor. If they struggle with that, that suggests proximal myopathy. Maria, how about you?

Dr Fleseriu: I completely agree. I always asked for pictures and the fellows are looking at us how it goes through Facebook to look at significant changes over time. The pattern is very important, the specifics, but also something that doesn't make sense. If a patient has diabetes and hypertension for years and suddenly, while taking the treatment became completely uncontrolled. For a younger women that had 2 fractures already, we have to think about the secondary cause. Then of course, I'm sure Rich will talk about it, for patients that have an adrenal tumors or they have other reason to screen for Cushing, but they are some that are features that are more important than others, let's put it this way.

Dr Auchus: The discriminatory features are the classic wide purple non-blanching striae greater than 1 cm. You can put your finger in them, and they don't blanche. But unfortunately these are rare and only occur in young people less than 40 years old. If you're only screening people who have those, you're missing a lot of people. Easy bruising is a big tip off, but this is common in Cushing, but it's also common if people are taking anticoagulation or even daily aspirin. Proximal muscle weakness, as Beverly mentioned, is a specific finding, but you have to examine the patient. This is a point I will make is that people send me lab tests and say, "Hey, does this patient have Cushing?" And I say, "Well, what is their physical exam show?" Osteoporosis can be specific, especially when it's unexpected. Obese people tend not to get osteoporosis. If you see a premenopausal person with obesity and osteoporosis, that should be a red flag. The point is that these are all catabolic features. Cortisol is a catabolic hormone that breaks down skin, muscle and bone. The skin, you see dermal atrophy, and I look for this and every patient sent to me, how thick are the ripples on the back of their hand? You have to examine the patient. The skin and the muscle, you can do that even on a video visit. You can ask the patient to squat down in front of the camera. You can have them squeeze the skin on the back of their hand and see what it looks like. It's the muscle weakness that causes the fatigue in these patients. I already mentioned osteoporosis and fertility factors. Then for adipocytes, it's the fat redistribution that they have disproportionate accumulation of fat in their head and neck area and that leads to the facial rounding, the disproportionate, particularly supraclavicular, fat pads. You should be able to see the divot behind the clavicle in a normal weight individual. The dorsocervical fat pad, or the buffalo hump, is not as specific. We already mentioned venous thromboses, poor wound healing, frequent infections. Then if they have an adrenal tumor, particularly if it's greater than 2.5 centimeters, that's a smoking gun. It needs to be investigated further.

You might want to ask how common is neoplastic hypercortisolemia, as we currently also call endogenous Cushing syndrome? There was a study in 13 centers in Spain called CRISALIDA study. What they did is they took people with at least 2 features compatible with Cushing syndrome, obesity, poorly controlled blood pressure despite at least 2 drugs, uncontrolled diabetes, hirsutism and menstrual disorders, and osteoporosis. They screened 353 of these patients who are probably garden-variety patients in your clinics with an overnight dexamethasone suppression test, and a late night salivary cortisol.

What they found is of these 7.4% had Cushing syndrome, 20 were ACTH-dependent and 6 were ACTH-independent, and other studies have confirmed that at least 3% of patients with poorly controlled diabetes have proven Cushing syndrome. What were the key predictive factors? Myopathy number 1, osteoporosis number 2, dorsocervical fat pad number 3, but obesity and type 2 diabetes by themselves were actually negative predictive factors. In other words, what you should be looking for in addition to these metabolic complications are those catabolic complications of Cushing syndrome on the muscle, the skin, the bone, and the redistribution of the adipocytes. How do you screen? We recommend usually 2 tests. Easy for you to do is a 1 mg overnight dexamethasone suppression test. This can be done anywhere. It has high sensitivity, picks up greater than 95% of patients, but it has only fair specificity, maybe 80% to 85%. Not all your patients will have the disease and the lower your pretest probability, the more likely an abnormal result is a false positive. Then you pair that with a late night salivary cortisol. Usually we get 2 or 3 on different days. It has a very high sensitivity for ACTH-dependent Cushing, about 98%, not as good for ACTH-independent Cushing, but that's where the dexamethasone suppression test is better. It also only has fair specificity. This is easy for the patient to do, but you need to have it done by a competent referral laboratory. And then the 24-hour urinary free cortisol is cumbersome. It has poor sensitivity, but good specificity. We generally don't recommend that primary care doctors get this as a first line test. A normal 1 mg dexamethasone suppression test is less than 1.8 µg/dL. We often measure dexamethasone levels as well to confirm that the patient took the drug and had the appropriate exposure. The late-night salivary cortisol less than a 100 ng/dL is normal, but abnormal has to be over about 200, 250 ng/dL. Then if you have 2 positive tests, we measure ACTH to see if it's low or if it's high. Then I would say that you recommend a referral to an endocrinologist if both tests are positive or if 1 test is positive and you have a high index of suspicion because of an abnormal result, or if people have an adrenal tumor and an abnormal dexamethasone suppression test. I think with that we'll go back to Maria to talk about centers of excellence.

Dr Fleseriu: Before moving to that, I wanted to point out that I agree with the tests you are using, and this is my preference too, but I wanted to point out that there are caveats to each test besides the normal values that are essential. Doing an overnight dexamethasone test on a woman who is on an oral estrogen, it's going to impede their results. Doing salivary cortisol at night in patients who are working at night and they have different cycles. It's very important, of course, for the urines or even more specificity of the test related to kidney function and a lot of other. So the normals are normal, but the caveats of the tests sometimes are even more important. Before we talk about center of excellence that I think should be the future for treating all the patients with Cushing disease at least once a year to be seen, I would like to hear from you, when do you think that the patients with suspicion for Cushing should be sent from the endocrinologist to a pituitary center? Then we'll make a case for what is the pituitary center.

Dr Biller: I would say whenever the endocrinologist thinks that they would like some help. We see patients sometimes where the endocrinologist has done absolutely everything in exactly the order that Rich outlined and the answer is clear, and I'll call them and say, "You did a great workup. How come we had the fun of seeing the patient?" Sometimes they'll just say, "Well, I don't see very much of Cushing and I just wanted to be sure that I was doing it right." From our perspective, being a teaching hospital with lots of fellows, that's terrific. Also the patients enjoy the opportunity to be at a center where we see lots of patients with that disorder. It used to be, before COVID-19, that they could sit in the waiting room and talk to other patients and be reassured that their condition isn't so rare.

In our center right now, we have other ways of providing that information. But I would say any time that the referring physician just feels that they would like some help. I do agree with Rich that discrepant results are always a time to get another opinion because it's hard to make the diagnosis.

Dr Fleseriu: It's hard, even for us. How about you, Rich? What do you think we should all do to improve awareness of the disease, but also referral for patients with discordant results and that they want a second opinion to the pituitary centers?

Dr Auchus: I think it's clear that results from surgery depend on the experience of the neurosurgeon. If the endocrinologist does not have access to an experienced neurosurgeon, that's a reason for referral to a center of excellence for pituitary diseases. That, and again, when it's unclear, if the diagnosis is correct or not.

Dr Fleseriu: I completely agree. The definition of a center of excellence is having a multidisciplinary approach. So not just the neuro-endocrinologist and the neurosurgeon that are vital, but patients sometimes have large pituitary tumors. We need a neuro-ophthalmologist. A reading of the pathology is essential -- a neuropathologist that knows how to differentiate between corticotropic adenoma vs grouped cell changes that could be a more aggressive tumor and other specialties, including specialized nurses, that are a tremendous help in discussing with the patients, especially for them that it's a rare disease overall. Their doctors tell them that maybe you're my first or second patient. It is essential for them to be plugged in with other patients and with providers that makes them feel more comfortable.

Dr Biller: Great. Well, I think we're out of time. I want to thank you both so much, Rich and Maria, for sharing your thoughts and wisdom about this challenging condition. I would like to thank those of you who've participated in this program. We're really excited that you want to learn about this disorder because we believe that recognition is more than half the battle to getting the right diagnosis and getting the patient to treatment. Please proceed to answer the questions in the post-activity assessment to receive your credit and take a moment to complete the program evaluation.

We hope that you have enjoyed it as much as we have. Thank you.

This transcript has been edited for style and clarity.

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