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Applying Advances in Practice: Case-Based Look at Selecting Therapy for Cushing Syndrome

Announcer:
Welcome to CME on ReachMD. This activity is the second in a series titled “The Cortisol Reports.” This is episode two, titled “Applying Advances in Practice: Case-Based Look at Selecting Therapy for Cushing Syndrome,” is provided by Cornerstone Medical Education and the American Academy of CME and is supported by an educational grant from Corcept Therapeutics.

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Dr. Blevins:
This is CME on ReachMD. I’m Dr. Lewis Blevins. I’m the Director of the California Center for Pituitary Disorders at the University of California in San Francisco. Joining me to discuss Cushing syndrome management and walk through some real-world patient cases is Dr. James Suliburk. Dr. Suliburk is the Chief of Endocrine Surgery at Baylor Hospital and Medical Center in Houston, Texas. Dr. Suliburk, thanks for being here today.

Dr. Suliburk:
Thanks, Dr. Blevins. It’s a pleasure to be here.

Dr. Blevins:
To start off, Dr. Suliburk, tell me about a recent patient you saw, and let’s use that patient to talk about, assessing for surgery, determining success rates, et cetera.

Dr. Suliburk:
Sounds good, Dr. Blevins. So, straight from the clinics last week, I saw a 72-year-old male. The guy’s a former retired firefighter, obese, BMI of 43, but had a really significant, amount of past medical history and medical comorbidities. Unfortunately, he’s one of those patients that when you see the, Epic screen, it just keeps scrolling and scrolling and scrolling on the EMR with the medication list. And as a surgeon, when I see these patients, I immediately understand that, well, this person probably has hypercortisolism because it takes all these different medications to treat the ravaging effects of cortisol on the body.

Dr. Blevins:
With regards to what we refer to in medicine as polypharmacy, is there something that can be done to improve this patient’s, likelihood of having a successful surgical operation?

Dr. Suliburk:
Yeah, absolutely. So these patients who, are on multiple different medications to symptomatically control the effects of hypercortisolism, I feel strongly that they can be optimized by simply treating the root problem, and that is the elevated cortisol levels. So, if we can get control of their cortisol and treat them with some anti-cortisol agents, that will generally allow them to have improved glycemic control and to lose weight, in preparation for undergoing adrenalectomy. Now, fortunately, adrenalectomy is now in a minimally invasive operation, so we’re very fortunate, to have that, those tools at our disposal; but even patients who undergo minimally invasive

adrenalectomy, they definitely tremendously benefit from preoperative medical optimization so they can lose some weight, get better hypertension control, better glycemic control, and have a much more, straightforward and rapid recovery postoperatively.

Dr. Blevins:
Now, your patient had, a low DHEA sulfate, a low ACTH, and failed the dexamethasone suppression test. That seems to me as if this patient clearly has the adrenal disease, and I believe you found a 2 cm right adrenal lesion for this particular patient, so, I presume the plan would be to do surgery on that right adrenal.

That's very well said, and I think that most people don't recognize is that both of these procedures are remarkably significant advances compared to the old-fashioned open adrenalectomy, where patients were in the hospital for 7 to 10 days after surgery and had extensive pain, so I'm really grateful that you can do these type of operations for our patients.

Can you tell us about any data regarding successful treatment?

Dr. Suliburk:
Yeah, so in our hands we have more than a 95% success rate for performing minimally invasive adrenalectomy. Our conversion rate is actually less than 5%, and our patients are durably cured more than 90% of the time with just that unilateral resection. So we take great effort to characterize their disease process appropriately, image them appropriately, and, and so the patient has sort of been preoperatively characterized both biochemically and radiographically, to guide us in our decision-making and help us have those enhanced outcomes and those gold standard outcomes postoperatively.

Dr. Blevins:
So, how do you approach the postoperative patient? How do you monitor to see if their Cushing's is improved? Obviously, patients who have a cortisol factory in an adrenal gland that suppressed the pituitary and the patient can have postoperative central adrenal insufficiency for a period of time. Give us an idea how you approach those patients to sort through those, postoperative endocrine issues.

Dr. Suliburk:
Yeah. So I think in, in the classic profound hypercortisolism patient, it's pretty straightforward. We're going to, perform that adrenalectomy and then overnight and postoperatively, we're going to expect that we're going to do glucocorticoid replacement on those patients. We do still, measure cortisol levels postoperatively. Once they drop, less than 10 and we start to see a little bit of a softening blood pressure, we're immediate to institute glucocorticoid replacement therapy. And we know that probably nine times at least out of 10 for that profound hypercortisolism patient, they will need steroid replacement, postoperatively with glucocorticoids. I think the more challenging area that we are seeing right now is how do we determine the need for glucocorticoid replacement in a mild hypercortisolism patient? And that's something I'd like to maybe get your thoughts on. And we keep all these patients in the hospital overnight for observation. We want to measure those cortisols. And then the next morning we're doing, ACTH stim testing on them to determine, the adequacy, of that remaining adrenal gland and cortisol function.

Dr. Blevins:
Well, I think you have a great approach to that, matter. Obviously, you're talking about the patients with mild autonomous cortisol secretion, or MACS, and who have evidence of what, what I like to refer to pathologic cortisol secretion but not hypercortisolism, but maybe relative hypercortisolism relative to what their normal set point would be, and it is important to address those issues. I tend to look at the morning cortisol, as you do. In general, based on some research that I'd done at another institution years ago, people with cortisol levels less than, less than 7 probably need steroid replacement. Between 7 and 12, they need further testing. Over 12, they probably wouldn't need hormone replacement at that time. I like to use the low-dose ACTH stimulation test. I use 1 mcg. I know some have used 5 mcg. Both are better than the 250 mcg test. I think it's 6 on one hand, half a dozen on the other way that you go with 1 or 5. I happen to do 1 because I did research on that many years ago and found that, that low-dose test in normal people will get the same kind of a rise you'll get for cortisol from the adrenals as a 250 mcg test. And I think it's a good sort of predictor of those who have mild adrenal suppression, maybe the level of adrenal suppression that requires hormone replacement.

I tell some physicians, at other centers that just treat the patient with a replacement dose of steroids and then reassess at four to six weeks later is another approach that one could do. Replacement doses shouldn't suppress the HPA axis, so you should be able to discontinue therapy and recheck, with a low-dose ACTH stimulation test at about two to three days after. I don't have a problem with doing it in the postoperative period. Most patients don't want to take steroids if they don't need them, so the sooner you resolve it, the better.

Dr. Suliburk:
Yeah, I think I love that approach and, certainly a very data-driven approach, to incorporate into that postoperative management. I think

one thing to touch on that, you know, us as surgeons that we face is that oftentimes our anesthesiologists are used to giving Decadron in the induction regimen for these patients, and it's important that we realize that, really there's no need to give Decadron as a "stress dose," when we're operating on these, hypercortisolism patients. Some, some sort of historic stories and historic antidotes and a little bit of historic data may have indicated that there's a potential for hyperacute adrenal crisis, during the resection if you didn't give steroid doses. We have not found that to be the case whatsoever. And in fact, when we give that Decadron with the induction, it clouds our ability to track cortisol measurements in that first 24-hour, period because we don't know how that HPA axis is really responding. Yes, we know we're getting cortisol levels, but we don't know how they've been thrown off by the exogenous dexamethasone that's been given, so we make sure that we don't allow any induction steroids to go when we do these cases. And then I really enjoy the data-driven approach of cortisol levels and the low-dose ACTH stim test should we need to perform it.

Dr. Blevins:
I think those are all good points, and I think they apply especially to the MACS patient and those with mild disease, which seem to be the ones that are being more commonly detected nowadays because of a heightened awareness, and they certainly don't need a huge dose of dexamethasone or any other steroid for that matter prior to a successful operation.

Dr. Suliburk:
Absolutely.

Dr. Blevins:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Lewis Blevins, and today I'm speaking with Dr. James Suliburk about the real-world management of Cushing syndrome. We spoke a bit earlier about determining if a patient is a surgical candidate and pretreatment before surgery, so now let's dig into medical management strategies before I present a recent patient I saw in my clinic.

So, with regards to potential medical management options for this patient, Dr. Suliburk, how would you proceed, or what do you see your endocrinologist doing to help you prepare a patient for a surgery, if they decide to treat the patient with severe hypercortisolism before you take them to surgery?

Dr. Suliburk:
Yeah, absolutely. So I really—we work in a multidisciplinary team with our endocrinologists, and, as opposed to titrating the blood pressure medications or titrating, other symptoms of hypercortisolism-based medications, we want to institute anticortisol therapy for these patients. And, we'll work, to understand what comorbidities the patient has and, with the regimens, if there's any other drug interactions that could happen, and then we'll start with anticortisol agents at a low dose to start prepping that patient and moving that patient towards, surgery. And, there's a number of different agents, that we can use and oftentimes it's sort of very nuanced and individualized with the patient as to which direction we'll go.

Dr. Blevins:
I approach it the same way. I think that every patient is different, and you can't treat any two patients just alike or get into the rut of saying, "Here are guidelines; here are recommendations; here's the first drug we should use;", "the second drug," for example. I think you have to individualize care, and use one of those drugs that either inhibits cortisol synthesis or blocks the effects of cortisol, for example.

I have had a couple of people ask about "Why don't you just treat me with medications instead of go to surgery?" And one of my colleagues, who's in, Italy, has actually done some research and showed that patients have a better outcome if you operate than treat long term with medical management or simply try to focus on managing the hypertension and the diabetes and the other consequences of the disease. So I do believe that surgery is, indicated, for all of these patients with adrenal pathology, but with that said, I think that it's useful sometimes to try to get patients, managed before surgery so they have the better outcomes that we discussed earlier.

Dr. Suliburk:
With all that being said, Dr. Blevins, tell me about a recent patient that you've seen in your clinics.

Dr. Blevins:
Well, this is a 36-year-old woman who had a prior history of Cushing's, no question about it. She underwent surgery. She had an ACTH immunopositive tumor, the proof in the pudding, so to speak. Her postoperative cortisol was 1 mcg/dL, indicating she had adrenal insufficiency, and we take that to usually mean that a patient has been rendered disease-free. The data are that if your cortisol is under 2, about 96% of patients will be in long-term remission. She required steroid supplementation for about two years until her pituitary adrenal function returned to normal. She lost 45 pounds in that year. And once her adrenal function recovered, her urine cortisol was 18. And then she was lost to follow-up and ultimately came back to see me, and at that time had insomnia and weight gain just wasn't feeling herself, but couldn't describe it other than those being her two main complaints. She had no Cushingoid features on examination

whatsoever, and her 24-hour urine cortisol now is up to 41, which was normal but was double of what she had before.

I did some testing and proved that she had, persistent, or really recurrent disease. We call it persistent, but they were in remission, but basically, once that residual, microscopic tumor, returns, they end up with progressive hypercortisolism. And I did an MRI, and I didn't see any evidence of a recurrent tumor yet, so she had biochemical evidence of, recurrence, and that sort of leaves us with not a surgical or radiotherapeutic options. We have to dive into the world of medical therapy for a patient like this.

Dr. Suliburk:
What medical options are there for people like this?

Dr. Blevins:
Well, there are a number of different treatments that are designed to sort of hit different, I should say, molecular targets. We can use somatostatin analogues, which can inhibit, ACTH release from a pituitary tumor, even though we don't see the tumor. That will lower ACTH, and that, will lead to less stimulation of the adrenal glands, and cortisol levels will fall. We can use a drug on the other end of the system and block the effects or modulate the effects of, cortisol on body tissues, and that drug is known as mifepristone. And those are relatively new therapies to sort of either inhibit ACTH production or block cortisol action— or modulate cortisol action is a better term—or we can use a drug to interfere with adrenal production of cortisol. And there are a number of drugs, including ketoconazole, mitotane, metyrapone, osilodrostat, and, Recorlev, so we have a number of other things there that we can use.

We tailor therapy individually. So, for example, if a patient has a large residual tumor—maybe they had a macroadenoma, which is greater than a centimeter, and the surgeon couldn't get it all out—we might actually try to use a somatostatin analogue inhibit ACTH because sometimes we can actually decrease the size of the tumor. If a patient has significant adrenal hyperplasia, I tend to favor using the adrenal biosynthesis blockers in that setting, and, usually will choose, ketoconazole or levoketoconazole as a first-line agent. The new drug osilodrostat is a drug that's also effective. I tend not to use metyrapone, and mitotane just because they're difficult drugs to obtain and to use, and patients don't tolerate them very well. If a patient doesn't respond to one of those drugs, I'll usually go to, to a different one and sometimes use two therapies. I've had a number of people that have taken ketoconazole and, the old drug metyrapone, which is similar to osilodrostat today. So sometimes you have to use two drugs. I tend to use mifepristone in patients that have very severe hypercortisolism and, life-threatening infections and things of that nature to modulate cortisol action.

One of the things I'd like to highlight is the importance of a team approach to the management of these patients.

Well, that's a great way to round out our discussion on the management of real-world patients with Cushing syndrome. I want to thank my guest, Dr. James Suliburk, for helping us to better understand how to care for patients before, during and after surgery. Dr. Suliburk, it was great speaking with you today.

Dr. Suliburk:
Thanks, Dr. Blevins. Tremendous. Thank you.

Announcer:
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