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Diagnostic Delay and the Critical Role of Personalized Screening Approaches in Cushing's Syndrome

Announcer:
Welcome to CME on ReachMD. This activity, titled "Diagnostic Delay and the Critical Role of Personalized Screening Approaches in Cushing's Syndrome" is provided by Prova Education.

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Dr. Fleseriu:
On average it can take 2 to 5 years for a patient to be accurately diagnosed with Cushing's syndrome. We will discuss how to tackle the diagnostic delay and improve patient outcomes.

This is CME on ReachMD, and I'm Dr. Maria Fleseriu.

Dr. Reincke:
And I'm Dr. Martin Reincke.

Dr. Fleseriu:
So let's dive right in. Martin, can you explain the significant diagnostic delay we're seeing for patients for Cushing's syndrome?

Dr. Reincke:
Unfortunately, it takes 2 to 5 years until a patient is finally diagnosed, and it's much too long, and it impacts on the comorbidities a patient is going to develop. Why is this? There's, of course, the aspect of lack of awareness in general. It's a rare disease, and therefore not everyone may be aware that it's existing. Then there're progressive features of the disease; so initially it may be rather oligosymptomatic and becomes, over time, to be more prominent. And then there's testing complexity, which makes it also quite difficult for rightly diagnosing Cushing's syndrome. And as I mentioned, diagnostic delay leads to an increase in severe comorbidities: diabetes, hypertension, osteoporosis, infectious diseases and psychiatric disorders. And therefore, it would be very interesting to diagnose the patients earlier.

Dr. Fleseriu:
I completely agree. And I think the testing complexity plays, also, an important role, as you mentioned, because it's harder for us. And we'll discuss also, later, which is the best test in the appropriate scenario for a particular patient is probably the most important question in addition to who to screen. So appropriate screening is an important aspect of reducing the time it takes to diagnose a patient.

Martin, you and your team recently studied the data from the German Registry regarding who we should be screening for Cushing's syndrome – the most important questions. What can you tell us about the findings from that study, as well as recommendations from our recent literature review?

Dr. Reincke:
Very good question. So first of all, I would like to start that the most frequent cause of Cushing's syndrome is exogenous steroid use, and this is something you always have to exclude and the patient may not be aware of that. Therefore, you have to carefully take the history and to make sure that the patient did not receive, for example, injections into the joints with long-acting steroids.

Otherwise, in terms of clinical features, it's very important that you are aware of unusual features which generally do not appear in younger patients. For example, osteoporosis in female patients or a combination of symptoms which are typical for Cushing's syndrome, like myopathies, skin changes like easy bruising or striae, the reddishness of their face, but also the metabolic complication. And then patients with adrenal incidentaloma, so adrenal masses detected by CT or MRI also. A group where you should suspect or you should exclude Cushing's syndrome.

Dr. Fleseriu:
That's very important, because once we decide who we should screen and then which is the best test, there are a lot of other features that can increase the risk of having high cortisol without actually being Cushing's, and it has to be also excluded, and sometimes it's easier to say than do it. The advice that I would have for practitioners is if you think the patient has Cushing's, once the exogenous glucocorticoids are excluded, we should rule that out. It's very important.

Dr. Reincke:
Yeah. Thank you, Maria. I would like also to add, if I may, that we have also this psychiatric comorbidity. So patients with increasing anxiety and depression can have Cushing's syndrome, and one has to look for that. And then the recent weight gain is also a quite typical symptom, not the long-existing obesity, but those patients who in the last couple of months have increased their weight. That is something where you should suspect Cushing's syndrome.

Maria, I have a question to you. The longer Cushing's syndrome goes undiagnosed, the greater the potential impact on mortality and morbidity. There can be complications related to cardiovascular disease, infections, fractures, depressions, and other sequelae. Once we have identified the patients we should be screening, what do we do next? What tests are recommended for screening?

Dr. Fleseriu:
Thank you, Martin. That's a very important question, and I don't have just one answer because when we're talking about screening, we have 3 types of tests for screening per se. We have 1-mg dexamethasone suppression test, 24-hour urinary free cortisol, and late-night salivary cortisol for screening, and then we have some tests for confirmatory testing. First and foremost, we have to rule out exogenous glucocorticoids, and we have to ask the patients if they're taking any type of steroids. Sometimes they're injections, sometimes they're creams, they are interarticular injections, so this is first.

And then how do we choose which type of screening versus the other depends on a patient's characteristics and also what's available at the local laboratory lab. So in general, I like to do the screening with late-night salivary cortisol. I do it a few nights in a row. It's much easier for the patient. However, for example, healthcare workers that are working days, nights, days, nights, this is not a good test because it's measuring the circadian rhythm. These would be the patients that I would do other tests, for example, the overnight dexamethasone test, we always measure the dexamethasone level. But if a woman is on estrogen with birth control pills or any other type of oral estrogen, the cortisol could be falsely elevated because of the binding protein that's increased. So again, it's not the best test. We can stop it before screening; I don't like to stop the birth control pills for 4 to 6 weeks. And then there are some laboratories that don't have a late-night salivary cortisol, so then we have to do the urinary free cortisol. Patients with renal failure cannot have urinary free cortisol because it's misleading. And of course, more than one collection, it's not easy for the patient. That's why it's called 24-hour urinary free cortisol. So everything needs to be measured throughout the day and we need at least 2 to 3 collections because we know the variability could be up to 50%.

And then for adrenal tumors, the most sensitive test is the overnight dexamethasone test.

So how do you do the screening in Germany, Martin?

Dr. Reincke:
Oh, thank you. We are doing it very similar, and I would like to add only that if you use the dexamethasone suppression test, it can be helpful to measure the dexamethasone at the same time. That increases the interpretability of the test. Also, I would like to add that sometimes renal function is impaired in patients, and then urinary free cortisol is not such a good test, and then we rather switch to dex suppression test or late-night salivary cortisol. I think most important is really that you repeat tests, especially if their results are not clear from the start and if there's high grade of suspicion because the cyclicity of the test results is one of the challenges we are facing.

Dr. Fleseriu:
I agree. The confirmatory testing is very important. Sometimes we repeat the same tests we did before. We have some other tests that we use for confirmatory testing, the desmopressin test. We used to have CRH [corticotropin-releasing hormone] tests that were combining with dexamethasone, but now it's not available anymore.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Maria Fleseriu, and here with me today is Professor Martin Reincke. We're discussing the diagnostic delay in Cushing's syndrome and the critical role of screening when there's clinical suspicion

for hypercortisolemia.

So let's assume we're done with screening; the patient had abnormal labs. We did confirmatory testing. Now what do we do to find out where the Cushing's is coming from, Martin?

Dr. Reincke:
Well, if it is confirmed biochemically and if also the clinical phenotype is indicating Cushing's syndrome, then you use imaging as a first step to establish the diagnosis. But before you do that, ACTH [adrenocorticotropic hormone] levels are the most important step. The ACTH is either high-normal or elevated in ACTH-dependent Cushing's or it's suppressed in adrenal Cushing's. And this is a switch which you can use. If ACTH is upper normal limit or elevated, then you will be doing an MRI of the pituitary gland, because pituitary Cushing's is most likely the diagnosis. If the ACTH is suppressed, then you do an imaging of the renal gland as a next step. And in ACTH-dependent Cushing's here we have ectopic Cushing's syndrome which can mimic pituitary Cushing's more or less 100%, and this is a difficult differential diagnosis. You need the specialized center there.

Dr. Fleseriu:
So, Martin, we did a screening. We did confirmatory testing and localization. What is next?

Dr. Reincke:
Well, if you have established the diagnosis, then you have achieved an important step. However, several issues are ahead of you. First of all, the question is whether the patient is severely sick, and that you can see by your test results. So if the biochemical screening is indicating very high urinary free cortisol, let's say above 1,000 µg/day, or the serum cortisol is also very high, like above 30 µg/dL, normal range until 25, then you know that the patient is very ill and needs immediate treatment and that in such a situation the patient should be referred immediately to a tertiary center for administering drugs.

So I would say look again at the test results. Make sure that to classify if the patient needs immediate treatment, needs soon treatment, or you may have even some more delay.

Maria, what do you think about this if the test and everything is positive?

Dr. Fleseriu:
So what I usually have in my mind, I have the pretest probability. So then I already have a plan even before getting their lab results, like you're mentioning, how bad this is both clinically and biochemically. And definitely, we are a tertiary center; we move to treatment as fast as we can. But what I think is very important, in addition to the treatment for Cushing's per se, either pituitary surgery or adrenal surgery or sometimes even neuroendocrine tumor secreting ACTH, is managing the comorbidities, because these patients have Cushing's for many years, and even patients with not-so-severe biochemical tests end up having a lot of comorbidities from psychiatric disorders, cardiovascular disorders. And the ones you mentioned earlier that are very severe are a higher risk of infections, and we have to treat to prevent that, are also now – we found out that also patients with mild Cushing's have higher risk of hypercoagulability, and this is almost 18 times higher than in normal population. So these patients with severe disease have to be anticoagulated. Now do we have to anticoagulate more patients even with mild Cushing's and when to start and how long to continue after surgery, I think the jury is still out on that. But definitely, in the patients that have severe disease, we have to manage the comorbidities including cardiovascular disorders also in parallel. So don't wait for the Cushing's to be treated. All of this has to be done in parallel and sometimes even before we treat the Cushing's.

Well, this has certainly been a fascinating conversation. But before we wrap up, Martin, can you share one take-home message with our audience?

Dr. Reincke:
Be aware of Cushing's syndrome. So look out, watch out for abnormal symptoms indicating endogenous hypercortisol, like skin changes, osteoporosis, metabolic complications in combination. And screen appropriately using 1 of the 3 screening tests which we have been discussing.

Dr. Fleseriu:
And after we do the screening, confirmatory testing in some patients is very important then to try and find out where this is coming from because there are many places where either cortisol or ACTH can start from. And then manage the patient appropriately both with treatment for Cushing's and also treatment of comorbidities.

That's all the time we have today, so I want to thank our audience for listening in and thank you, Dr. Martin Reincke, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. Reincke:

The pleasure is on my side. Thank you very much, Maria.

Announcer:
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