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Tackling Diagnostic Delay in Cushing's Syndrome

Announcer:

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Dr. Reincke:

This is CME on ReachMD, and I'm Dr. Martin Reincke. Here with me today is Dr. Maria Fleseriu.

A recent meta-analysis of 44 studies found a mean of 2.8 years between symptom onset and Cushing's syndrome diagnosis. Maria, what does this diagnostic delay mean for our patients, and what can we do better in our clinics to shorten this time to diagnosis?

Dr. Fleseriu:

That's a very important question, Martin, and I don't know if we have the perfect answer, but we should definitely try because this diagnostic delay for most of the patients is increasing the risk of comorbidities. Sometimes it's increasing even the mortality rates. So this is very important to tackle earlier. And also the reversibility of the comorbidities. So some patients will never return to normal from quality of life or other comorbidities such as hypertension or diabetes just because they had the Cushing's for so long. So we know that. Now how we change it in screening earlier, it's getting to be much harder; it has to be a multidisciplinary effort. So from a primary care point of view, if a patient comes with some clinical features that corroborate an increased risk of having Cushing's, that patient has to be screened. Now how to screen this patient depends on patient's characteristics. So we have several screening tests. We are using late-night salivary cortisol, urinary free cortisol in 24-hours that's measuring how much gets excreted in the urine, and also how the cortisol responds to dexamethasone by the overnight dexamethasone test. Each of these tests have some specific characteristics and are better for some populations than others. So for example, in women that are on birth control pills, oral dexamethasone suppression test is not the best test unless you stop the estrogen. If you work nights, then the late-night salivary cortisol that's measuring the circadian rhythm is also not the best test. If you have renal failure in a patient, then it's harder to use the 24-hour urinary free cortisol. So there are some pitfalls of each of the tests, but the best sensitivity and specificity, and also what's very interesting, the best preferred for patients also is the late-night salivary cortisol.

So when we have all these tests, we need usually more than 2, and each of the late-night salivary cortisol and urine, also, more than 2 or even 3 times sometimes. After that, if they are positive, we go to confirmatory testing, and then from there, we have to move to localization. So we have to find out where the Cushing's is coming from so we can really address with appropriate treatment, and the treatment for most causes of Cushing's is surgery, either pituitary surgery or adrenal surgery, or if we're lucky and find a neuroendocrine tumor, taking out. Few patients will need medical therapy before surgery because we can't find the tumor, but in general, that's what we tell patients. Yes, the testing is cumbersome, but we need to find out as soon as possible where this is coming from and then to refer the patient to a tertiary center and also to surgery, a specialized surgeon, at the same time.

Dr. Reincke:

Thank you, Maria, this was awesome. So what would be the first step to delineate the origin of Cushing's syndrome? Which test would

you use there?

Dr. Fleseriu:

So that depends on the ACTH, and that's very important to have a good assay for ACTH. If the ACTH is low, then it's easy because we have to do a CT of the adrenals. However, if the ACTH is high normal or is sometimes even normal, then we think this is ACTH-dependent Cushing's. But again, very important to be in a good assay. And then if the patient – we'll do an MRI of the pituitary – the patient has a pituitary tumor that's more than 6 to 10 mm and it's a younger woman, the probability would be to be Cushing's disease. If not, most of the tumors for patients with Cushing's disease are very tiny, sometimes not even visible, as you know, we have to do petrosal sinus sampling to make sure. Because the risk of that being a pituitary incidentaloma is very high. So seeing something on the MRI doesn't mean that the Cushing's is coming from there. So we need more tests to make sure before we send the patient to surgery.

Dr. Reincke:

Thank you, Maria. This was awesome. I think in summary it's important that you may run into a situation where you are not sure whether the patient has Cushing's or not Cushing's. In such a situation you should transfer the patient to an appropriate center. Another situation where you should refer it is if the patient is severely sick, especially if the cortisol is really very high, because then the patient is at high risk of further complications.

Well, this has been a great bite-sized discussion. Thanks for listening.

Announcer:

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