

# DIAGNOSTIC TESTS FOR MILD CUSHING'S SYNDROME

Cushing's syndrome is a rare disorder which occurs when there is an overproduction of the hormone cortisol from the adrenal glands. One cause of this syndrome is Cushing's disease which is a benign tumor located in the pituitary gland. The tumor produces excess Adrenocorticotrophic Hormone (ACTH) which causes the adrenal gland to secrete excess cortisol. Our study examined 101 possible Cushing's syndrome patients with symptoms such as weight gain, weakened muscles, and sleep disturbances. Out of the 101 patients, 28 patients are Cushing's confirmed, 39 patients are excluded from the syndrome, and 34 patients are unclear of the syndrome due to further testing being run. Multiple tests such as the chair test, a pituitary MRI, salivary tests, and a night-time urine Cortisol/Creatinine Ratio were utilized to see which test was the best to correctly diagnose the syndrome. Multiple tests were performed because in a previous study, Dr. Friedman showed how no single test is completely effective in immediately diagnosing or excluding Cushing's syndrome. Our preliminary results show the night-time urine Cortisol/Creatinine Ratio is the best single test to correctly confirm Cushing's syndrome, but even this test needs to be done with other tests.

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## BACKGROUND

Cushing's syndrome is a relatively rare endocrine disorder caused by the over production of the hormone cortisol in the human body. Cushing's syndrome was discovered by and named after Dr. Harvey Cushing, an American neurosurgeon. He reported malfunctions in the pituitary gland and described this syndrome in his work *The Pituitary Body and its Disorders*. When stress arises, the hypothalamus releases corticotrophin-releasing hormone, which triggers the anterior of the pituitary gland to release adrenocorticotropin hormone (ACTH). ACTH is produced in a process by which proopiomelanocortin (POMC) is synthesized. Lastly, ACTH stimulates the adrenal glands to secrete the vital hormone cortisol. However, in Cushing's disease, there is a pituitary tumor which makes too much ACTH causing excess cortisol secretion.

Cortisol is the most potent glucocorticoid, a hormone that metabolizes fats, proteins, and carbohydrates. Cortisol is involved in the production of blood cells, functioning of muscles, normal responses to the immune system, normal functioning of the heart, and regulation of insulin. During the process of cortisol being produced, if there is an adrenal or pituitary tumor or disorder, excess cortisol will be secreted, which is a characteristic of Cushing's syndrome.

With cortisol being so vital, Cushing's syndrome has catastrophic consequences when diagnosis is delayed. Cushing's syndrome can cause high blood pressure, osteoporosis, and diabetes. Without proper diagnosis, more health complications can arise, as well as death.

## METHODS/MATERIALS

During a period of one year, 101 participants were evaluated; 28 of whom were Cushing's confirmed, 39 of whom were Cushing's excluded, and 34 needed more testing for proper diagnosis. The participants took the following tests: pituitary MRI, chair test, night-time free cortisol/creatinine ratio, and salivary cortisol tests. The participants' results were organized and recorded in a spreadsheet. We analyzed data from only the Cushing's confirmed and excluded participants. The confirmed and excluded were compared to one another.

MRI's were taken of the pituitary gland to observe a possible adenoma in the pituitary or adrenal gland. Both Cushing's confirmed and excluded participants took multiple nighttime salivary tests, which reflect free cortisol levels in the serum. Cortisol levels are lower at nighttime, but Cushing's patients have higher levels. The normal range for the salivary tests is 4.3 nmol/L or lower. A higher level infers that the patient may be diagnosed with the syndrome.

For the chair test, the participants stepped up and down five times and the time it took them to perform the task was recorded in seconds. Participants who were unable to perform the task received a time of 0 seconds. This test was performed to observe patients' muscle strength. In Cushing's patients, muscle weakness is a major symptom. The average and median of the times were taken for both Cushing's confirmed and excluded participants.

The nighttime free cortisol/creatinine ratio calculated the cortisol levels in 10 hr urine from 10 pm-8 am. The ratio cut-off range was 16. With ratio

values  $>16$ , it is hypothesized that participants can be diagnosed with Cushing's syndrome.

## RESULTS

Of the 28 confirmed participants, 24 had results for the free cortisol/creatinine ratio. Ten of the participants had values of  $\geq 16$ , which is above the cut-off line. While 14 participants had ratio values  $<16$ , 7 excluded participant had ratio values  $>16$  and 16 excluded participants had ratio values  $<16$ .

All 28 Cushing's confirmed participants participated in the chair test. The average test value was 14.4 and the median was 13. Similarly, all 39 Cushing's excluded participant participated in the chair test. The average test value was 15 and the median was 14.

Twenty six Cushing's confirmed participants took at least one salivary test. Five participants have at least one value  $>4.3$  and 25 participants had at

least one value  $< 4.3$ . As for the Cushing's excluded participants, 25 participants had at least one salivary test value. Three participants had test values  $>4.3$  and 25 participants had test values  $<4.3$ .

Seventeen Cushing's confirmed participants had an MRI. Six participants had adenomas and their sizes were 2 mm, 3 mm, and 4 mm. Twenty two Cushing's excluded participants had an MRI. Three of the participants had adenomas and the sizes were 2 mm and 3 mm.

## DISCUSSION

The free cortisol/creatinine ratio, salivary test and chair test did not perform well in confirming the syndrome in the study. Most ratio values were negative for confirmed participants and its sensitivity was  $<50\%$  at 41.7%, while its specificity was 69.6%. The majority of the salivary test values were negative for the confirmed participants.

The chair test did not show any changes between the confirmed and excluded group of participants. However, the tests showed consistency in excluding the participants from the disease even though some patients were confirmed Cushing's patients, which proves how one test can not effectively confirm or exclude the syndrome.

The pituitary MRI test was the most effective test in confirming Cushing's disease. More than 50% of the confirmed had a pituitary adenoma, which is one of the major causes of Cushing's syndrome. The sensitivity of the pituitary was 61.5% compare to the 41.7% sensitivity of the free cortisol/creatinine ratio. Furthermore, the specificity for the pituitary MRI was 30.3%. Most adenomas were small ranging from 3–4 mm in size.

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