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Secondary Adrenal Insufficiency: Diagnosis, Treatment, Complications and Black Box Warnings

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1. Abstract:

Secondary and Primary Adrenal Insufficiency are rare endocrine pathologies. Symptoms include: diarrhea and/or constipation, rib pain (asthma like symptoms), vomiting, dizziness leading to decreased balance, brain fog, fatigue, major weight loss, flank pain, and mood complications (caused by lack of fight or flight) which leads to the body being on hyperdrive by working harder to compensate for low cortisol and increased mast cell activity as a compensatory mechanism. Secondary Adrenal Insufficiency is diagnosed through a process of testing the levels of hormones integral to the stress response, namely adrenocorticotropic hormone (ACTH) and cortisol. Adrenal crisis, caused by Secondary Adrenal Insufficiency are extremely rare but can occur. Common causes are: inhaled steroids, steroid injections and oral steroid usage. This can be prevented by putting a patient on steroid replacement therapy using prednisone or hydrocortisone. Cushing Syndrome, however, is the other extreme of SAI. Cushing Syndrome is too much cortisol production. The symptoms of Cushing Syndrome are rapid weight gain, more than normal fat deposits, stretch marks, and fatigue. One of the most reliable ways to diagnose Cushing Syndrome is an 8:00 AM cortisol check. Often treatments for Cushing Syndrome are, reducing steroids, removing steroid producing tumors, and transsphenoidal surgery. Considering all of this, a Black Box Warning may be necessary. A Black Box Warning is a warning put on a drug that warns about the major health complications it may cause. Black Box Warnings should be considered for drugs that cause Secondary Adrenal Insufficiency. With a black box warning, patients and their caregivers will be aware that these medications lead to Secondary Adrenal Insufficiency.

2. Introduction:

Secondary Adrenal Insufficiency (SAI) is extremely uncommon and there is a dearth of research and data in the medical literature. However, Secondary Adrenal Insufficiency is more common than Primary Adrenal Insufficiency (PAI), with a prevalence of 150-280 per million, while Primary is 93-144 per million (2). Addison's disease, which can also be diagnosed as Primary Adrenal Insufficiency, affects 100-140 of every million people. Women are more likely than men to develop Addison's. This condition mostly occurs in ages 30-50 years, but can occur at any age, even childhood. Secondary Adrenal Insufficiency, on the other hand, occurs in those with certain conditions that affect the pituitary gland (1). When looking at children and inhaled corticosteroids hypothalamic–pituitary–adrenal axis suppression is a problem that develops when the hypothalamic-pituitary-adrenal (HPA) axis—a complex relationship between the hypothalamus, the pituitary gland, and the adrenal glands—is overtaxed. The HPA axis was

suppressed in 9.3% of cases in a cohort of 214 children using inhaled corticosteroids (9). PAI may be caused by autoimmune (Addison's disease), surgical, hemorrhagic, ischemic, or metastatic etiology. In contrast to PAI, SAI may be caused by traumatic brain injury, tumors, and hemorrhagic/ischemic lesions of the hypothalamic-pituitary axis, but also by chronic glucocorticoid treatment lasting more than 3-4 weeks, even including topical administrations like aerosols for asthma and COPD or creams used for skin problems (4). Black Box Warnings should be considered for drugs that cause Secondary Adrenal Insufficiency. With a black box warning, society will be aware that these medications lead to Secondary Adrenal Insufficiency. The purpose of this paper is to review the existing literature on SAI, with a particular focus on its under-discussed causes and symptoms. The paper will conclude with an argument for developing a black-box warning on medications that contribute to SAI.

3. Symptoms of Secondary Adrenal Insufficiency:

The most common symptoms of SAI are diarrhea and/ or constipation, vomiting, brain fog, fatigue, flank pain, and mood changes (caused by lack of fight or flight) which leads to the body being on hyperdrive by creating more effort to compensate for low cortisol and mast cells starting in as a compensatory mechanism. (1), (2), (3), (5), (7) Less common symptoms can include asthma-like symptoms, dizziness leading to being unbalanced, and major weight loss. (1), (2), (3), (5), (7) Each person experiences a different cluster of symptoms and it varies from case to case. However, what is normal for one person's symptoms may not be the same symptomatology for another. The major issue that can occur if SAI is not treated and addressed in proper time is an Adrenal Crisis. This can lead to severe complications like organ failure and a coma-like state that leads to death. Adrenal Crises may be triggered by infections, malcompliance stress (physical and emotional), and surgery.Adrenal Crises may also be caused by heat and possibly gastrointestinal issues (neither has been researched).

3.1 Secondary Adrenal Insufficiency causes:

The main known causes of SAI are inhaled steroids, steroid injections and oral steroid usage (2), (3), (4), (5), (9) . This can most commonly be seen in a wide range of patients being treated for arthritis with steroids, cancer patients, and even everyday healthy presenting individuals who are on inhaled steroids for asthma. That being said, SAI is more commonly seen in cancer patients and patients getting arthritis treatment than those taking inhaled steroids (9), (10), (11), (8).

3.2 Diagnosing process:

SAI is commonly diagnosed through a process of testing levels of ACTH and cortisol (1), (2), (3), (4), (5), (9). Other providers may opt for additional testing of basic metabolic hormones and other hormones within the body. This is because some individuals who lack cortisol can have SAI caused by improper hormone balance. Dehydroepiandrosterone (DHEA) is a prime example. Additional tests run are MRIs and CAT scans to check for cancerous tumors in the body. The reason ACTH is tested with cortisol is because it shows if the person has Primary or Secondary Adrenal Insufficiency. MRIs and CAT scans are done to check for cancer because cancer can cause the body to go into Adrenal Insufficiency. When it comes to pituitary tumors, low corticotropin secretion occurs. For hypothalamic tumors, low corticotropin-releasing hormone occurs (5).

4. Adrenal Crisis Diagnosis:

The severity and symptomatology of Adrenal Crisis is heterogeneous, which adds to the difficulty of diagnosis. It is estimated that 5-17 cases of Adrenal Crisis happen per every 100 patient years per patient with Primary or Secondary Adrenal Insufficiency (4). Symptoms of this are nausea/vomiting, fever, altered consciousness, hypotension <100mmHg systolic, hyponatremia <132mmol/l, hyperkalemia, hypoglycemia, hypercalcemia, along with low cortisol, which is usually less than 10 ug/dL (1), (2), (3), (4), (11), (8).

4.1 Prevention and Treatment of Adrenal Crisis:

Adrenal Crisis can be prevented by putting a patient with SAI on steroid replacement therapy, which is done with either prednisone or hydrocortisone (hydrocortisone is most preferred because it most closely mimics cortisol

production). (1, 2, 3, 4, 5, 6, 7) Some patients may use a steroid pump, but most take it orally. Once an individual shows symptoms of Adrenal Crisis, most providers recommend using a solu-cortef injection of 100mg of steroid to lessen the severity and prevent major complications. (2, 4, 9) Treatment varies on how well the individual absorbs the steroid. Individuals who struggle to absorb orally taken steroids will most likely be put on a cortisol pump (which pumps cortisol directly into the body like an insulin pump). This is because steroids, which are used to replace cortisol in the body to keep an individual stable when not absorbed, may lead to Adrenal Crises, which may lead to more major complications such as death. (1, 4, 5, 9, 11) The goal of treatments like these is to stabilize the patient and prevent Adrenal Crisis. This is in hopes that the individual can then continue to lead as typical of daily life as possible.

5. Complications and Causes of Cushing Syndrome:

It is necessary to know about Cushing Syndrome due to it being the other end of SAI. Too much cortisol production leads to Cushing Syndrome. This can be caused by inhaled steroids used for treatment or general steroids. Cushing Syndrome can be seen in patients with human immunodeficiency virus and/or pneumonia seeking treatment using steroids (8), (12). However, this can happen as well in individuals receiving steroid treatment for cortisol replacement. One way a patient develops Cushing Syndrome is when the HPA axis and the adrenal glands communicate properly again, which leads to the adrenal glands producing adequate levels of cortisol. When a patient is creating normal cortisol in addition to taking steroid replacement, too much cortisol can occur. The normal range is 3.0mcg/dL-30.0mcg/dL (8), (12). Most endocrinologists argue that until cortisol levels are greater than 25, Cushing Syndrome will not be considered along with symptoms of Cushing Syndrome. The problematic nature of this can be the balancing act of treating SAI and finding proper dosage without causing this complication.

5.1 Symptoms of Cushing Syndrome:

The most common symptoms of Cushing Syndrome are rapid weight gain, more than normal fat deposits, stretch marks, and fatigue. The patient can feel just as bad as they did when having SAI as when they have Cushing Syndrome (12).

5.2 Diagnosis:

The most reliable diagnosis route is getting an early morning cortisol check upon waking because a patient's cortisol will be the highest in the morning than any other time (2, 9). Paying attention to these symptoms will allow a baseline for diagnosis of Cushing's syndrome. The primary care physician needs to be aware that the individual is having these symptoms so they can refer them to an endocrinologist to help manage this issue. The doctor's awareness brings the best chance of a proper diagnosis.

5.3 Treatment of Cushing's Syndrome:

Treatments for Cushing's Syndrome are reducing steroids, removing steroid producing tumors, and transsphenoidal surgery. The other option often considered alongside these is a healthier diet, namely cutting out carbs and junk foods. This will vary from case to case and what works best for one individual may not work for another, which is why there are a variety of options depending on the treatment the individual is receiving. Some individuals may try one or multiple approaches at once until they find what works best for them.

6. Why a Black Box Warning is needed:

A black box warning is a warning put on a drug that warns patients and providers about the major health complications it may cause. Certain medications used in the line of treatment may cause tendon damage, secondary adrenal insufficiency, death, or other complications. Very often these medications do not have black box warnings. With a black box warning, society will be aware that these medications can lead to Secondary Adrenal Insufficiency. It serves as a halt and stop kind of label so that people will take time to understand the side effects of the medication.

6.1 Medications Black Box Warnings should be considered for**:**

Black Box Warnings should be considered for drugs that cause Secondary Adrenal Insufficiency. The medications are solu-cortef injections, flovent, hydrocortisone, prednisone (2), (3), (4), (5), (9) . This can most commonly be seen in a wide range of patients being treated for arthritis with steroids, cancer patients, and asthma patients. It is extremely rare for adults to develop SAI from inhaled steroids when compared with children (9).

6.2 How to Get a Black Box Warning**:**

Reporting incidents to the FDA is the best way to have a drug be considered for a Black Box Warning. You can report it through the FDA's phone number, email. Also by mailing address. The FDA will then decide if the incident is enough for the drug that was taken to be given a warning. When that happens the FDA will either fast track it or do a Black Box Warning at a normal rate. This will vary on a case-to-case basis. It also varies based on what the FDA deems necessary incident wise for a black box warning to be placed on a medication.

7. Conclusion:

Secondary Adrenal Insufficiency, although not extremely common, is more prevalent than Primary Adrenal Insufficiency. Secondary Adrenal Insufficiency is diagnosed primarily through serum testing of cortisol levels. Secondary Adrenal Insufficiency can lead to complications like Adrenal Crisis. Prevention of this and treatment for Secondary Adrenal Insufficiency is primarily done with oral steroids. When in crisis they will treat it with 100mg Solu-cortef injection. The flip side of this is too much cortisol, which leads to Cushing Syndrome. The treatment for this is lower steroid usage, surgery, and a healthy diet. There should be more research on Secondary Adrenal Insufficiency. Black box warnings should also be considered for drugs that cause Secondary Adrenal Insufficiency to make patients aware of this complication.

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