Department of Veterans Affairs
Office of Inspector General

Office of Healthcare Inspections

Report No. 14-04505-346

Healthcare Inspection

Diagnosis and Treatment of a Patient's Adrenal Insufficiency at a Virginia VA Medical Center

August 25, 2016

Washington, DC 20420

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Executive Summary

The VA Office of Inspector General (OIG) Office of Healthcare Inspections conducted a review to assess allegations of misdiagnosis of Addison's disease and adverse outcomes resulting from long-term steroid treatment in a patient with multiple medical problems.

We substantiated that the patient's electronic health record problem list first reflected the patient had Addison's disease in 2004 although laboratory tests did not support this diagnosis. The patient received steroid medications after developing signs and symptoms of adrenal insufficiency in 2004. Because steroid medication was the appropriate treatment option for adrenal insufficiency that was caused by either Addison's disease or another disease process, the patient received appropriate care at the time the steroids were initially started.

Between 2004 and 2006, providers were not able to assure routine follow-up of the patient due to irregular use of VA health care services. When the patient re-established routine care with a VA primary care provider in 2007, actions should have been taken to reassess the patient and confirm the adrenal disease-related diagnosis.

Ultimately, a comprehensive evaluation of the patient's medical history, co-occurring conditions, lab and imaging tests, and medication actions and interactions was completed in 2012 and an endocrinologist was able to wean the patient off chronic steroid therapy.

We could not substantiate the allegation that the patient experienced adverse health events including avascular necrosis of the hip joints solely as a result of prolonged steroid treatment for adrenal insufficiency. The patient had a complex medical history, and we believe the most likely cause of the avascular necrosis and need for bilateral hip replacement was a combination of long-term steroid use and the various treatments used to manage other comorbidities.

We made one recommendation.

Comments

The Veterans Integrated Service Network and Facility Directors concurred with our recommendation and provided an acceptable action plan. (See appendixes A and B, pages 9–11 for the Directors' comments.) We will follow up to confirm completion of the corrective action.

JOHN D. DAIGH, JR., M.D.
Assistant Inspector General for
Healthcare Inspections

Purpose

The VA Office of Inspector General (OIG) Office of Healthcare Inspections conducted an inspection to assess allegations of misdiagnosis of Addison's disease and adverse outcomes resulting from long-term steroid treatment. The purpose of this inspection was to determine if the allegations had merit.

Background

Adrenal Insufficiency

The adrenal glands are small glands located on top of each kidney that produce hormones necessary for life. Two hormones that are produced in the adrenal glands, cortisol and aldosterone, belong to a class of hormones called corticosteroids. Cortisol, the "stress" hormone, regulates how the body converts fats, proteins, and carbohydrates to energy; helps regulate blood pressure and cardiovascular function; regulates immune response; and suppresses inflammatory reactions. Aldosterone maintains the right balance of salt and water while helping control blood pressure. Patients with adrenal insufficiency commonly complain of fatigue, nausea, anorexia, and weight loss. Other common clinical findings include hypotension (low blood pressure), hyperkalemia,[1] and hyponatremia.[2]

Various disease processes or medications may cause adrenal insufficiency. Primary adrenal insufficiency, also known as **Addison's disease**, occurs when at least 80–90 percent of the cortex of the adrenal gland is damaged and cannot produce enough cortisol and/or aldosterone. The most common causes of Addison's disease are autoimmune destruction of the adrenal glands, bilateral adrenal hemorrhage, and other infectious diseases.[3]

Secondary adrenal insufficiency is more common than Addison's disease and occurs when the pituitary gland in the brain fails to produce enough adrenocorticotropic hormone (ACTH), a hormone that stimulates the adrenal glands to produce cortisol. Causes of secondary adrenal insufficiency include changes to the pituitary gland (for example, surgery or radiation) and discontinuation of synthetic corticosteroids used to replace cortisol and aldosterone (referred to as steroids in the remainder of this report).

Adrenal crisis (severe, acute adrenal insufficiency) is a life-threatening emergency that is often triggered by a stressful event such as surgery, a severe injury, or an illness. Adrenal crisis usually manifests with nausea, vomiting, abdominal pain, and shock. In

[1] Hyperkalemia is an abnormally elevated level of potassium in the blood.
[2] Hyponatremia is a condition in which the amount of sodium (salt) in the blood is lower than normal.
[3] About 70 percent of reported cases of Addison's disease are due to autoimmune disorders in which the immune system makes antibodies that attack the body's own tissues or organs and slowly destroy them. See National Institute of Diabetes and Digestive and Kidney Diseases, "Adrenal Insufficiency and Addison's Disease." Accessed on April 9, 2015, from http://www.niddk.nih.gov/health-information/health-topics/endocrine/adrenal-insufficiency-addisons-disease/Pages/fact-sheet.aspx.

most cases, symptoms of adrenal insufficiency become serious enough that people seek medical treatment before an adrenal crisis occurs. However, symptoms sometimes appear for the first time during an adrenal crisis.

Complexity of Diagnosing Causes of Adrenal Insufficiency

Addison's disease and secondary adrenal insufficiency may be differentiated through measurement of the plasma ACTH level. An ACTH stimulation test is used to measure the level of cortisol in the blood before and after an injection of synthetic ACTH (cosyntropin). ACTH stimulation tests show the output of cortisol in response to synthetic ACTH and are done in conjunction with plasma cortisol levels taken at different times of the day. These tests need to be completed according to a strict protocol; otherwise, the results may not be definitive. Interpretation of plasma ACTH levels must be done in the context of simultaneous plasma cortisol levels.

A patient's comorbid conditions and/or treatments may make diagnosing adrenal insufficiency challenging. Furthermore, identifying the causes of adrenal insufficiency can be complicated. In complex cases, appropriate laboratory testing and further clinical evaluation in the context of the patient's total medical profile is indicated. For example:

- Adrenal insufficiency can be a complication of many different disorders. It is often difficult to exclude the diagnosis of adrenal insufficiency in patients with other concurrent disorders based on the "clinical picture" because many of these patients have nonspecific symptoms and signs such as weakness, weight loss, and hypotension.
- Medications can interfere with adrenal function by reducing metabolism of systemic steroids which may lead to Cushing's syndrome[4] and secondary adrenal insufficiency.
- Prolonged use of steroids is known to cause secondary adrenal insufficiency because the adrenal glands produce less of their natural hormones. When prescription doses of steroids are stopped, the adrenal glands may be slow to restart their production of the body's glucocorticoids. Patients taking oral steroids for an extended period of time (for example, greater than 30 days) are at risk for acute adrenal insufficiency if they suddenly stop the medication. This paradox of the treatment causing the condition further confuses the differential diagnosis.

Treatment

Regardless of whether patients have Addison's disease or secondary adrenal insufficiency, treatment of acute adrenal insufficiency involves replacing cortisol with steroids (typically dexamethasone, hydrocortisone, or prednisone). Patients with Addison's disease (generally more permanent adrenal insufficiency) require life-long steroid replacement therapy. Patients with temporary adrenal insufficiency may only

[4] Cushing's syndrome is a rare condition that occurs when there is excess cortisol in the body.

require steroid replacement therapy until the cause of the condition is identified, treated successfully, and/or resolved and the patient can be safely tapered from the medication.

Scope and Methodology

We conducted a review from March through June 2015. We interviewed the patient at issue as well as the primary care and endocrinology providers who last saw the patient.

We performed an extensive review of the patient's electronic health record (EHR) spanning care provided at three VA medical centers (VAMC-1, VAMC-2, VAMC-3) from 2003 through 2013. We also reviewed documents provided by the patient and pertinent medical literature.

In the absence of current VA/VHA policy, we considered previous guidance to be in effect until superseded by an updated or re-certified Directive, Handbook, or other policy document on the same or similar issue(s).

We **substantiate** allegations when the facts and findings support that the alleged events or actions took place. We **do not substantiate** allegations when the facts show the allegations are unfounded. We **cannot substantiate** allegations when there is no conclusive evidence to either sustain or refute the allegation.

The inspection was conducted in accordance with the *Quality Standards for Inspection and Evaluation* published by the Council of the Inspectors General on Integrity and Efficiency.

Case Summary

At the time of our review, the patient had multiple medical problems including diabetes and had been receiving intermittent care at VAMC-3 for more than 18 years.

2003–Mid-2004

In 2003, the patient relocated. In early 2004, while attending an appointment at VAMC-1, the patient became weak, hypotensive, and complained of abdominal pain. He/she was transported to the emergency department (ED) and was subsequently admitted to an intensive care unit. Blood and urine cultures were negative for infection. Head and abdominal computed tomography were negative for pituitary and adrenal gland abnormalities and hemorrhages. During this admission, the patient was started on prednisone in preparation for a dental procedure.

Because of persistently low blood pressures recorded during the patient's hospitalization, the provider ordered an ACTH stimulation test to rule out adrenal insufficiency. The patient received a steroid medication prior to the ordering of the ACTH stimulation test. The ACTH test was never completed because the baseline (pre-injection) blood sample, drawn the previous day, could not be used. The plasma cortisol levels were interpreted as being consistent with adrenal insufficiency. Upon discharge, the provider prescribed a steroid medication to be taken twice daily and entered an endocrinology consult request.

During a post discharge endocrinology appointment, the patient reported not complying with the twice-daily steroid dosing due to his/her living situation and requested a once-daily dosing schedule. The endocrinologist changed the patient's medication to once daily and scheduled a follow-up appointment for approximately 2 months hence.

Several days after the post discharge endocrinology appointment at VAMC-1, the patient was admitted to VAMC-2, thus missing the scheduled follow-up endocrinology appointment at VAMC-1. The patient did not complain of symptoms suggestive of an adrenal crisis during this VAMC-2 stay. The patient received a daily steroid (as originally prescribed by the VAMC-1 endocrinologist) and other medications related to his/her chronic disease processes during this time. A physician assistant added "Addison's Disease (ICD-9-CM 255.4)" to the patient's EHR problem list. The patient was discharged approximately 2 months later.

Mid-2004–2012

The patient again relocated and saw an outpatient clinic physician for the first time to establish care and to secure an "adrenal insufficiency kit."[5] Shortly thereafter, he/she was hospitalized and seen by a newly assigned primary care provider (PCP-1) and other physician specialists for his/her underlying chronic medical problems during this hospitalization. The patient saw PCP-1 several months after discharge at which time, PCP-1 documented that the patient reported improvement of "Addison's disease" while

[5] An adrenal emergency kit includes self-injectable hydrocortisone to prevent adrenal crises.

taking a daily steroid medication. PCP-1 also documented, "Flexion at the hips is very slow and painful." Although PCP-1 requested the patient return to clinic in 2 weeks, the EHR reflects that, other than an ED visit, the patient did not return to the facility for almost a year.

When the patient did return to VAMC-3 in late 2005, he/she reported running out of medications "4 months ago." PCP-1 reordered the medications and transferred the patient's care to another primary care provider (PCP-2), to be seen the following month.[6]

During an early 2006 appointment, PCP-2 documented that the patient reported being compliant with his/her medications and feeling better after restarting a steroid medication. In late 2006, the patient was admitted to the facility for complications related to diabetes. The patient was discharged 6 days later on twice daily steroid medication. Lab values remained consistent with adrenal insufficiency.[7]

In 2007, the patient began to participate more consistently in treatment and follow-up of medical needs. PCP-2 consulted the endocrinology service to assist with treatment of the patient's adrenal insufficiency. Due to multiple cancellations by the clinic and several patient no-shows, the patient was not seen. During this time, the patient was noncompliant with taking his/her medications. The patient was also diagnosed with bilateral avascular necrosis (AVN) of the hip; however, he/she was not a candidate for hip replacement at that time due to poorly controlled diabetes. In late 2007, the patient reported compliance with taking medications but developed an infection that required a prolonged hospital stay. A low ACTH stimulation test result was consistent with adrenal insufficiency.

In 2008, PCP-2 re-consulted the endocrinology service, and the patient was seen the next month. During this appointment, the patient reported continuing to have reduced energy levels and muscle weakness since being discharged from a hospital the previous month and complained of significant pain in both hips. The endocrinologist noted the patient had a "cushingoid" (moon face) appearance and reduced the patient's steroid medication. At a 4-month follow-up visit, the patient complained of early evening fatigue, so the endocrinologist re-adjusted the patient's steroid medication. A low ACTH stimulation test result remained consistent with adrenal insufficiency.

In 2009, the endocrinologist ordered laboratory studies which confirmed poorly controlled diabetes and persistently low ACTH and cortisol. The endocrinologist changed the patient's medications several times to address daily fatigue cycles. The patient admitted to a poor diet and also reported taking two different steroid medications.

In mid-2009, the patient was admitted to the facility's intensive care unit for multiple acute medical problems. The patient reported not taking steroids for approximately 1 week. Three weeks after discharge from the hospital, he/she had a follow-up appointment with

[6] PCP-1 retired.

[7] Interpretation of these and subsequent lab values would have been unreliable for the purpose of diagnosing the cause of the adrenal insufficiency, partly because of the patient's medication regimen and treatment non-compliance. Providers were likely using these lab tests to monitor the patient's response to the changes in steroid therapies.

an endocrinologist. Laboratory studies reflected low potassium and ACTH values. The endocrinologist increased the patient's steroid medication for "suppressed ACTH." It was unclear whether the endocrinologist was aware that the patient reported previously not taking the steroid medication for a week. No medication changes were made during a subsequent 2009 endocrinology appointment.

The patient underwent bilateral hip replacements in 2010 and 2011. He/she continued to be followed by PCP-2 during this time.

The patient was also followed by a clinical pharmacist from 2009 through 2012 who routinely reviewed the patient's medications, compliance, and response. In an early 2012 progress note, the clinical pharmacist documented "pt [patient] is hit or miss with… [medication] for adrenal disease." The clinical pharmacist placed a new consult to the endocrinology service requesting an evaluation of the patient's management. Laboratory values reflected a low ACTH stimulation test result.

A few months later, a different endocrinologist completed a history and physical examination and performed an extensive EHR review. The endocrinologist documented that the patient had likely been misdiagnosed with Addison's disease and had been treated with steroids that were causing secondary adrenal insufficiency. The endocrinologist initiated decreasing doses of the patient's steroid medication and was able to eventually discontinue it altogether.

Inspection Results

Allegation 1: Misdiagnosis of Addison's Disease

We substantiated that the patient's EHR problem list first reflected Addison's disease in 2004 although laboratory tests did not support this diagnosis. The patient experienced symptoms that were consistent with adrenal insufficiency in early 2004. An ACTH stimulation test done in 2004 was not completed, but plasma cortisol levels were interpreted as a "suboptimal response." We noted, however, that interpretation of these lab values would have been unreliable, as the patient was already on steroid therapy. Additional laboratory testing was not completed.

During exams performed for admission at VAMC-2, the patient apparently told providers about a recent bout of adrenal insufficiency. It is unclear why the physician assistant added Addison's disease, rather than adrenal insufficiency, to the patient's problem list. We did not find evidence within the EHR that an appropriate diagnostic evaluation was completed to support a diagnosis of Addison's disease.

Because use of steroids was the appropriate treatment option for both Addison's disease and/or adrenal insufficiency from another cause, we concluded that the erroneous addition of Addison's disease to the problem list did not have a clinically significant impact on the patient's care *at that time*.

Treatment and Follow-Up (2004–2006)

Between 2004 and 2006, the patient's psychosocial circumstances and irregular use of health care services made testing and follow-up challenging. Specifically, the patient did not consistently receive care through a PCP or endocrinologist, which reduced the likelihood that the cause of the adrenal insufficiency would be investigated. During that time, the patient tended to seek treatment, and new steroid prescriptions, through ED providers or during hospitalizations for issues not related to an adrenal insufficiency problem.[8]

Treatment and Follow-Up (2007–2012)

In 2007, the patient re-established care with PCP-2, and over the next several years, was generally seen every few months. The patient also routinely saw an endocrinologist in 2008–2009.

Because steroid treatment of adrenal insufficiency is often a long-term commitment with potentially serious side effects, a definitive diagnosis of the cause for the adrenal insufficiency is paramount. Over the years, the patient's clinical presentation on several occasions was not consistent with what would have been expected if the patient had a clear diagnosis of Addison's disease (primary) or secondary adrenal insufficiency. Specifically, the patient reported having been off steroids for 1 week or more in 2005 and again in 2009. Despite complaints of fatigue and other non-specific issues at the time, he/she was not critically ill. The patient's history of non-compliance with steroid therapy, as well as an unusual (stable) presentation when steroids were stopped, should have prompted providers to reassess and confirm or rule-out the cause of the adrenal insufficiency.

Ultimately, a comprehensive evaluation of the patient's medical history, co-occurring conditions, lab and imaging tests, and medication actions and interactions was not completed until 2012. While the patient may have intermittently experienced bouts of adrenal insufficiency in previous years that required periodic steroid treatment, a new endocrinologist was able to wean him/her off chronic steroid therapy.

Allegation 2: Adverse Outcomes Due to Prolonged Steroid Treatment

We could not substantiate the allegation that the patient experienced adverse health events solely as a result of prolonged corticosteroid treatment that was ordered initially for signs and symptoms of adrenal insufficiency and later for a diagnosis of Addison's disease.

Numerous clinical studies show a relationship between long-term steroid use and AVN as well as other serious medical conditions. The patient's other underlying medical problems

[8] Under these circumstances, providers would be expected to address the patient's presenting problems, not discontinue the corticosteroids and initiate work-up of what appeared to be a reasonable diagnosis supported by laboratory and other clinical data.

may have contributed to an increased incidence of AVN. We could not determine which condition or treatment weighed most heavily in the development of AVN.

Conclusions

We substantiated that the patient's EHR problem list first reflected Addison's disease in 2004 although laboratory tests at the time did not support the diagnosis. The patient received steroids in 2004 after developing signs and symptoms consistent with adrenal insufficiency. Because steroid medication was the appropriate treatment option for adrenal insufficiency caused by either Addison's disease or another disease process, the patient received appropriate care at the time the steroid treatment was first initiated.

Between 2004–2006, providers were not able to assure routine follow-up of the patient's condition due to irregular use of health care services. However, when the patient re-established care with a VA primary care provider in 2007, actions should have been taken to reassess the patient and confirm adrenal insufficiency and possible causes of the insufficiency.

Ultimately, a comprehensive evaluation of the patient's medical history, co-occurring conditions, lab and imaging tests, and medication actions and interactions was completed in 2012 and an endocrinologist was able to wean him/her off chronic steroid therapy.

We could not substantiate the allegation that the patient experienced adverse health events solely as a result of prolonged steroid treatment for adrenal insufficiency and/or Addison's disease. The patient had a complex medical history, and we believe the most likely cause of the AVN and need for bilateral hip replacement was a combination of long-term steroid use and the various treatments used to manage other comorbidities.

Recommendation

1. We recommended that the Facility Director initiate a clinical review of this case and take appropriate actions to educate providers, if indicated.

VISN Director Comments

Department of Veterans Affairs

Memorandum

Date: November 4, 2015

From: VISN Director

Subj: Healthcare Inspection—Diagnosis and Treatment of a Patient's Adrenal Insufficiency at a Virginia VA Medical Center

To: Director, Atlanta Office of Healthcare Inspections (54AT)

Director, Management Review Service (VHA 10E1D MRS Action)

1. The attached subject report is forwarded for your review and further action. I reviewed the response of the VA Medical Center (VAMC) and concur with the facility's responses.

Original Signed by VISN Director

Facility Director Comments

Department of Veterans Affairs

Memorandum

Date: October 23, 2015

From: Facility Director

Subj: Healthcare Inspection—Diagnosis and Treatment of a Patient's Adrenal Insufficiency at a Virginia VA Medical Center

To: VISN Director

1. I have reviewed the draft and concur with the recommendations. The findings outlined in the OIG report reflect a thorough evaluation.

Original Signed by Facility Director

Comments to OIG's Report

The following Director's comments are submitted in response to the recommendation in the OIG report:

OIG Recommendation

Recommendation 1. We recommended that the Facility Director initiate a clinical review of this case and take appropriate actions to educate providers, if indicated.

Concur

Target date for completion: October 31, 2015

Facility response: The VAMC initiated a clinical review on the above case. The Chief of Medicine conducted a comprehensive clinical review on this case. The findings from the clinical review were communicated with the provider. In conclusion, the Chief of Medicine provided education to the provider.

Appendix C

OIG Contact and Staff Acknowledgments

Contact	For more information about this report, please contact the OIG at (202) 461-4720.
Contributors	Sherry Purvis-Wynn, BSN, MA, Team Leader Victoria Coates, LICSW, MBA Julie Kroviak, MD Joanne Wasko, LCSW Thomas Wong, DO Toni Woodard, BS

Appendix D

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