Case report

Secondary adrenal insufficiency after glucocorticosteroid administration in acute spinal cord injury: A case report

Huiqing Yang¹, Michelle Trbovich^{1,2}, Jeffrey Harrow^{1,2}

¹Department of Physical Medicine and Rehabilitation, University of Texas Health Science Center at San Antonio, TX, USA, ²Spinal Cord Injury Service, Audie L. Murphy Memorial Veterans Affairs Hospital, San Antonio, TX, USA

Context/background: A 61-year-old female with cervical stenosis underwent an elective cervical laminectomy with post-op worsening upper extremity weakness. Over the first 3 weeks post-op, she received two separate courses of intravenous steroids. Two days after cessation of steroids, she presented with non-specific symptoms of adrenal insufficiency (AI). Initial formal diagnostic tests of random cortisol level and 250 µg cosyntropin challenge were non-diagnostic; however, symptoms resolved with the initiation of empiric treatment with hydrocortisone. Ten days later, repeat cosyntropin (adrenocorticotrophic hormone stimulation) test confirmed the diagnosis of AI.

Findings: AI is a potentially life-threatening complication of acute spinal cord injury (ASCI), especially in those receiving steroids acutely. Only three cases have been reported to date of AI occurring in ASCI after steroid treatment. The presenting symptoms can be non-specific (as in this patient) and easily confused with other common sequelae of ASCI such as orthostasis and diffuse weakness. The 250 µg cosyntropin simulation test may not be the most sensitive test to diagnose AI in ASCI.

Conclusion: The non-specific presentations and variability of diagnosis criteria make diagnosis more difficult. One microgram cosyntropin simulation test may be more sensitive than higher dose. Clinicians should be aware that AI can be a potential life-threatening complication of ASCI post-steroid treatment. Prompt diagnosis and treatment can reverse symptoms and minimize mortality.

Keywords: Acute spinal cord injury, Steroid, Adrenal insufficiency, Cosyntropin stimulation test

Introduction

While high-dose glucocorticosteroid (steroid) administration in the setting of acute spinal cord injury (ASCI) in an attempt to improve neurological outcome, is no longer recommended as standard of care, it remains a treatment option until other therapies become available for clinical use.^{1,2} Steroid administration is also considered an acceptable therapy for cases with acute neurological deficits post-operatively.³ While pneumonia, wound infection, sepsis, and pulmonary embolism are known to occur at a significantly higher rates in persons receiving glucocorticoids within the first 48 hours after ASCI, a relatively uncommon, yet serious, adverse event is secondary adrenal

insufficiency (AI), a condition which most commonly occurs from exogenous steroid use; the risk of developing AI is strongly related to the dose administered.⁴⁻⁶ Presenting symptoms are often non-specific and can be difficult to distinguish from common sequelae of ASCI. Our patient, who is presented in this report, probably represents a case of secondary AI due to several days of administration of dexamethasone after elective cervical laminectomy.

Case report

A 61-year-old female with past medical history of hypertension, type 2 diabetes, hyperlipidemia, coronary artery disease, deep vein thrombosis, osteoarthritis, depression, and cervical and lumbar spinal stenosis. She underwent an elective C3–7 cervical laminectomy for severe cervical stenosis from C3–7 causing spinal cord compression with cord signal change at C6–7 causing frequent falls

Correspondence to: Michelle Trbovich, Department of Rehabilitation Medicine, UT Health Science Center San Antonio, Mail Code 7798, 7703 Floyd Curl Drive, San Antonio, TX 78229-3900, USA.
Email: Michelle.Trbovich@va.gov

and urinary incontinence. She had no history of previous steroid use. Pre-operatively, all standard muscle groups tested on the International Standards for Neurological Classification after Spinal Cord Injury (ISNCSCI) examination were 4–5/5 on the manual muscle test (MMT). She was independent in activities of daily living and ambulatory for short distances. Immediately after surgery, she received dexamethasone 4 mg intravenously (IV) every 6 hours for five doses; thus, the total dose of dexamethasone administered was 20 mg over a 30-hour period. On post-operative day (POD) 1, all muscle groups tested on ISNCSCI examination were 4–5/5. On POD 2, she developed a central cord syndrome, with new upper extremity weakness greater than lower extremity weakness. Left upper extremity MMT examination was 0/5 in the deltoid and biceps, 4/5 in triceps and hand intrinsics, and 5/5 in finger flexors. Right upper extremity MMT was 2/5 in the deltoid: 4/5 in biceps, triceps, and hand intrinsics, and 5/5 in finger flexors. Emergent magnetic resonance imaging (MRI) without contrast revealed C4–5 spinal cord compression with new cord signal changes, from posterior edema of paraspinal muscles. Emergent cervical wound exploration demonstrated edema of the subfascial paraspinal muscles with resulting cord compression, without hematoma or seroma. The muscle layer was left open, and a peridural drain placed. Post-operatively, she had persistent bilateral upper extremity weakness (left > right) with urinary retention and intact leg strength consistent with a central cord syndrome pattern. ISNCSCI examination was consistent with C3 ASIA Impairment Scale D tetraplegia. Follow-up MRI 1 week after the second surgical intervention showed persistent edema, for which she was restarted on dexamethasone 4 mg IV q6h on POD 9.

The dexamethasone was gradually tapered over the following 8 days (Table 1). On POD 19, 2 days after her last dexamethasone dose, during physical therapy, she suddenly developed acute neck pain, fatigue, nausea, and diffuse muscle weakness resulting in the inability to support her own head or to move her upper or lower extremities. Neurological examination was negative for mental status changes or focal deficits.

Her supine blood pressure was 61/33 mmHg. Laboratory analysis collected during the hypotensive episode revealed that the electrolytes, blood urea nitrogen (BUN), and creatinine values were within normal limits with a serum glucose concentration of 135 without the presence of acidosis. There was no leukocytosis, eosinophilia, or anemia noted. The electrocardiogram was unremarkable. A cortisol drawn during the hypotensive episode was 16 µg/dl (6.7–22.6). After receiving 1 l of IV normal saline over 60 minutes, her blood pressure rose to 120/67 mmHg. Anterior–posterior and lateral cervical radiographs showed no acute bony changes. The patient was started on hydrocortisone 50 mg IV every 8 hours for the presumptive diagnosis of secondary AI as a consequence of prolonged exogenous glucocorticoid administration. Twelve hours later, her strength returned to baseline, her nausea resolved, and her systolic blood pressure increased to 131/77 mmHg. Because of her clinical improvement with glucocorticoid replacement, but an apparently “normal” cortisol level during the acute episode, a 250 µg cosyntropin (Cortrosyn) stimulation test was performed 2 days after the episode, on POD 21, after holding hydrocortisone for 12 hours. The baseline cortisol level of 2.3 µg/dl increased to 15.7 µg/dl at 30 minutes and to 19.1 µg/dl at 60 minutes, which is normal based on a 30- or 60-minute value ≥ 18 µg/dl. Hydrocortisone was weaned over the following 6 days down to a daily dose of 15 mg (Table 2). Because of her rapid clinical improvement with dexamethasone administration, and the exclusion of other diagnoses to that would have explained her clinical presentation, the cosyntropin stimulation test was repeated on POD 32, after holding hydrocortisone for 12 hours; the repeat stimulation test revealed a baseline cortisol level of 4.2 µg/dl that increased to 13.0 and 13.7 µg/dl at 30 and 60 minutes, respectively, which is diagnostic of AI.⁷

At discharge from acute rehabilitation 3 months post-operatively, her strength had returned to her premorbid level of MMT 4–5/5 in all key muscle groups on ISNCSCI exam. Two months post-discharge, a repeat adrenocorticotrophic hormone (ACTH) stimulation test requested by an endocrinologist revealed a baseline serum cortisol value of 10.8 µg/dl that rose to 17.4

Table 1 Course of dexamethasone dose administration post-operatively

POD	0	1	9	10	11	12	13	14	15	16	17
Dexamethasone (4 mg IV q6h)	**	***	**	****	****	***					
Dexamethasone (2 mg IV q6h)						*	****				
Dexamethasone (2 mg IV q12h)								**	**	**	*

*, one dose.

(Note, steroids not given on PODs 2–8.)

Table 2 Course of hydrocortisone treatment after clinical diagnosis of AI from POD 19 to 27

POD	19	20	21	22	23	24	25	26	27
Hydrocortisone (50 mg IV q8h)	*	***	**						
Hydrocortisone (25 mg IV q12h)			*	*	*				
Hydrocortisone (5 mg PO qPM)					*	*	*	*	
Hydrocortisone (15 mg PO qd)						*	*	*	*

*, one dose.

and 18.9 µg/dl after 30 and 60 minutes, respectively, which was considered a borderline response, prompting the recommendation to place the patient on low-dose hydrocortisone (15 mg qAM) with routine follow-up evaluation. The patient was successfully weaned off hydrocortisone 19 months after initiation of glucocorticoid therapy without the recurrence of any symptoms of AI.

Discussion

To the authors' knowledge, only three cases of secondary AI from exogenous steroid administration in ASCI have been reported. Two cases presented with fever of unknown origin; one case presented with systemic hypotension requiring vasopressor support.^{8–10} Our patient presented with neck pain and nausea during physical therapy and symptoms of generalized weakness and hypotension (not requiring vasopressor support). All previously reported cases received only 23–34 hours of high-dose methylprednisolone at the time of admission. Our patient received 17 days of medium-dose steroids (dexamethasone 16 mg daily or less).

AI in ASCI can easily be overlooked, as similar non-specific symptoms occur frequently in ASCI. Up to 74% of persons with cervical SCI have persistent orthostatic hypotension (OH) during the first month following SCI.¹¹ There is also a high prevalence of neck pain associated with OH (75%) after SCI and 58.9% of persons with SCI have symptomatic OH during physical therapy, which is consistent with our patient's presentation.^{12,13} The symptoms of nausea, weakness, and hypotension could be caused by hypoglycemia, acute pancreatitis or other causes of an acute abdomen, or immobilization hypercalcemia. This patient did not have evidence of these conditions. Notably, this patient did not have any of the classic laboratory abnormalities associated with AI, e.g. hyponatremia, hyperkalemia, acidosis, or eosinophilia. AI was suspected based on the presenting symptoms, in the context of recent glucocorticoid administration. In retrospect, an apparently normal random cortisol level drawn during the episode of hypotension was misleading. The normal range for a random

cortisol is based on the assumption that the patient is at rest, unstressed, and with normal blood pressure. Since the cortisol level was drawn during a period of hypotension, it was inappropriately low.

AI in chronic SCI without glucocorticoid administration: incidence and pathophysiology

In persons with chronic SCI naïve to exogenous steroids, incidence of AI has been documented as high as 47–68%.^{14,15} Huang speculated that central neurotransmitters may be altered in patients with chronic SCI and that long-term impaired ACTH secretion may cause mild adrenal atrophy and, thereby, a reduced cortisol response to stress. Meanwhile, in spinal cord transected animals, it has been shown that sympathetic denervation of the adrenal gland results in reduced adrenal blood flow, impaired medullary catecholamine response to hemorrhage, and reduced cortisol secretion.^{16–18} The applicability of any of these pathophysiological changes of the chronic SCI setting to the ASCI setting is unknown.

AI in ASCI with and without glucocorticoid administration: incidence and pathophysiology

The incidence of AI in persons with ASCI with or without exogenous steroids is unknown, but likely rare. However, *in the presence of neurogenic shock*, AI is reported as high as 22%.¹⁹ While the pathophysiology of AI in ASCI in a steroid-naïve patient is unclear, it is well known that administration of exogenous steroids in ASCI has the potential to suppress the hypothalamic pituitary axis (HPA) function. This can occur as soon as a few days after steroid administration and is typically dose-dependent.^{20,21} Case reports demonstrate that only 24 hours of high-dose steroids predisposes persons to secondary AI.^{8–10,20} Our patient developed AI symptoms 2 days after completing 17 days of glucocorticoid administration. The three other case reports of patients with ASCI describe symptoms of AI starting at 4, 14, and 23 days after receiving just 24 hours of glucocorticoids.^{8–10}

Garcia-Zozaya reported a case in which symptoms of hypotension resistant to volume resuscitation and

vasopressor therapy presented 2 weeks post-ASCI and resolved with hydrocortisone. Initial and follow-up cosyntropin test weeks later were both diagnostic for AI.⁸ Despite the temporal association of improvement in clinical course in this patient with ASCI immediately following glucocorticoid administration who had recently received high-dose methylprednisolone according to the standard protocol, the author admitted to being “unclear” as to whether ASCI, proximate steroid administration, or pre-existing AI was responsible for the patient’s clinical presentation.⁸ Meanwhile, Weant *et al.*¹⁰ reported fever developing in a person with ASCI 23 days after injury where a 24-hour steroid infusion was given. Extensive infectious workup was negative; however, 1 µg cosyntropin stimulation test assisted in the diagnosis of AI and prompted the initiation of hydrocortisone that resulted in resolution of fever within 2 days. Finally, Lecamwasam *et al.*⁹ reported a case of fever, leukocytosis, and hypotension 4 days after ASCI in a patient who had received 24 hours of methylprednisolone infusion acutely. Extensive workup including infectious causes, echocardiogram, and thyroid studies was unrevealing, but cosyntropin test was diagnostic for AI. Hydrocortisone administration resulted in immediate resolution of fever and hypotension requiring vasopressors, Lecamwasam concluded that although a definitive causal relationship between the steroid administration and AI diagnosis was not established, “their temporal association and the elimination of other possible etiologies led us to postulate that the AI was a complication of the steroid protocol”.⁹ In summary, the paucity of literature reporting the incidence and pathophysiology of AI in the setting of ASCI suggests that it is relatively uncommon and may be difficult to definitively attribute the etiology of AI to antecedent steroid administration.

That said, the consequences of missing the diagnosis can be life-threatening. Pastrana *et al.*¹⁹ reported that in 199 steroid-naïve persons with ASCI, AI was identified in 8 of 199 (4%) patients (e.g. 8 of 37 patients who met the criteria for neurogenic shock had AI), and the diagnosis of AI carried a higher risk of complications ($P = 0.01$), including intubation ($P = 0.002$), and a non-significant risk increase in 30-day mortality (13 vs. 3%, $P = 0.39$). It is well appreciated that the consequences of failing to identify the diagnosis of AI can be life-threatening.²²

Diagnosis of AI in ASCI

The definitive diagnosis of AI in ASCI can be challenging. One criterion is a random cortisol <15 µg/dl.

The ACTH stimulation test is more sensitive and specific.^{7,22} The high-dose (250 µg) ACTH stimulation test is the standard test. A normal response is a rise in serum cortisol concentration after either 30 or 60 minutes to ≥ 18 µg/dl.²³ The high-dose stimulation test excludes primary AI (adrenal hypofunction), not secondary AI (hypothalamic pituitary dysfunction).^{24,25} There is evidence that the low-dose stimulation test (1 µg) may be more sensitive than the 250 µg test in diagnosing secondary AI.^{26–28} Wang and Huang¹⁴ found that in steroid-naïve persons with chronic SCI, low (1 µg) and high (200 µg) stimulation doses had sensitivities of 95.2 and 52.4%, respectively. In our patient, the first 250 µg test may not have been sensitive enough to diagnose secondary AI.

Alternative provocative tests to diagnose secondary AI include the metyrapone stimulation and insulin-induced hypoglycemia. The metyrapone was not formulary in our Veterans Affairs (VA) pharmacy and, as such, was not able to be administered. Meanwhile, the insulin-induced hypoglycemia test is relatively contraindicated in persons with a history of seizures, hypothyroidism, cardiovascular, or cerebrovascular disease. Our patient had a history of coronary artery disease, and, as such, an insulin tolerance test was contraindicated.

Treatment of patients who present in possible adrenal crisis should not be delayed while diagnostic tests are performed. It should be started immediately on clinical suspicion. The lack of hyponatremia and hyperkalemia should not be considered evidence against the diagnosis of AI, because the rapid onset of AI due to secondary causes may not result in deficient mineral corticoid release from an adequately functioning zona glomerulosa.

Conclusion

Patients with ASCI who have received steroids, as well as those who have not, are prone to the development of AI, an acute life-threatening condition whose clinical presentation can mimic other common sequelae of ASCI. Failure to presumptively diagnose and promptly treat AI may result in a poor outcome. Clinicians should maintain a high index of suspicion, and be prepared to administer appropriate glucocorticoid hormone therapy if symptoms consistent with AI should occur. Treatment with glucocorticoids will promptly reverse symptoms and allow for more effective participation in acute rehabilitation programs, as well as reduce potential mortality, especially in the presence of intercurrent illness.

Disclaimer statements

Contributors HY conceived the idea to write up the case report, collected the data via chart review, conducted the literature review, drafted the majority of the article, edited the article and approved the article for publication. MT assisted with data collection via chart review and interpretation of data, conducted the literature review, drafted the paper in part, performed extensive revisions, and approved the article for publication. JH reviewed the article critically for important intellectual content, did extensive revisions and approved article for publication.

Conflicts of interest None.

Ethics approval Since this article is a case report of one person, ethics approval was not required. We did however obtain signed consent from the patient to access her electronic record to write the report.

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