

High Prevalence of Adrenal Insufficiency in Patients with Sickle Cell Disease: Results from a Community Hospital in the U.S.

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Key words

- adrenal insufficiency
- sickle cell disease
- cosyntropin test

Abstract

Objective: Despite the low prevalence (0.008%) of adrenal insufficiency (AI) in the general population, this disorder was recently diagnosed in a substantial number of sickle cell disease (SCD) patients at our hospital. The main objective of this study was to assess the prevalence of AI in SCD patients.

Methods: All adult patients admitted to the Department of Medicine at Interfaith Medical Center from October 2010 to November 2011 were eligible for this retrospective study. Medical records of adult SCD patients hospitalized for painful crisis and who had undergone cosyntropin testing were reviewed. Adult non-SCD patients hospitalized for painful crisis and who had undergone cosyntropin testing served as controls. The result of the cosyntropin test was

the primary outcome. The prevalence of positive cosyntropin tests was compared between the 2 groups by using Student's *t*-test, and odds ratios.

Results: 62 adult SCD patients were enrolled in the study. 15 underwent cosyntropin testing and 12 (19.4%) of these patients were found to have AI. AI was also diagnosed in 1 of 1340 non-SCD patients. The odds ratio for AI in SCD to non-SCD patients [(12/62)/(1340)] was 259. The odds ratio for the prevalence of AI in SCD patients in our study (19.4%) vs. the general population (approximately 0.008%) was 2375.

Conclusion: AI occurred in 19.4% of SCD patients included in this study. These patients thus have a 2375-fold higher risk of developing AI than the general population, and a 259-fold greater risk of developing AI than do hospitalized non-SCD patients.

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Introduction

Adrenal insufficiency (AI) is a condition in which the adrenal glands do not produce adequate amounts of cortisol. It is a rare disorder that affects about 8 in 100000 (0.008%) adults [1]. Clinical symptoms include weakness, dizziness, low blood pressure, and hypoglycemia; however, the onset is usually insidious, and in such cases, plasma sodium and potassium abnormalities may be the only indicators of the disease. Recently, AI was diagnosed in a substantial number of patients at our hospital. Most of the affected patients had sickle cell disease (SCD) and had been admitted for sickle cell painful crisis management. The workup for AI is invariably triggered by findings of low blood pressure or electrolyte abnormalities without signs of sepsis, dehydration, or myocardial infarction. The aim of our study was to assess the prevalence of AI in SCD patients retrospectively by reviewing their medical records.

Subjects and Methods

Patients

The Interfaith Medical Center is a 287-bed community-based hospital in New York City. All adult patients (aged 18 years or older) hospitalized to the medical floor at the Interfaith Medical Center, between October 24, 2010, and November 23, 2011, were eligible for this retrospective study.

Inclusion criteria

Medical records of adult SCD patients (confirmed by hemoglobin electrophoresis) that were hospitalized for painful crisis, had low morning cortisol levels, and had undergone cosyntropin testing were reviewed. Medical records of adult non-SCD patients that were hospitalized for painful crisis, that is, any type of pain as a chief complaint, and who likewise underwent cosyntropin testing were also selected and used as controls.

	SCD		Non-SCD (Control)		p-value
number of Patients	62		3		N/A
age (Median years)	32.2 ± 10.6		27.7 ± 4.2		P = 0.45
female Gender (%)	38/62 (61%)		0/3 (0%)		N/A
Race (%)	-		-		N/A
black	58/62 (94%)		3/3 (100%)		-
white	3/62 (5%)		0/3 (0%)		-
others	1/62 (1%)		0/3 (0%)		-
underlying Disease	Hb-SS 33	33 (53%)	Substance Abuse	1 (33%)	N/A
	Beta-Thalassemia	14 (23%)	HIV/AIDS	1 (33%)	-
	Hb-SC	9 (15%)	HIV/AIDS	1 (33%)	-
	Other	6 (10%)			-

Table 1 General Demographic Characteristics of Patients.

Exclusion criteria

Patients younger than 18 years and those who had been treated with steroids for any reason other than AI within the last year were excluded from the study. Adult SCD patients hospitalized for painful crisis whose morning serum cortisol levels were greater than 18 µg/dL (exclusion criteria for AI) were excluded.

Study variables

The primary study variable was the result of cosyntropin tests. Secondary variables were: the doses of opioids administered during index admission, results of iron studies, and numbers of red blood cells units transfused over the previous year. Other co-variables were gender, age, genotype of sickle cell hemoglobinopathy, mean corpuscular volume (MCV), reticulocyte count, lactose dehydrogenase (LDH) levels, and blood pressure on test date.

Morning serum cortisol levels were measured between 0600 h and 0800 h for screening tests, and the results were analyzed as described below. AI was confirmed if the morning serum cortisol level were less than 3 µg/dL [2–4]. Diagnosis of AI was ruled out if morning serum cortisol levels were greater than 18 µg/dL [2,5]. For the patients whose morning serum cortisol levels were between 3 and 18 µg/dL, cosyntropin tests were subsequently conducted. Morning serum cortisol levels and plasma adrenocorticotropic (ACTH) levels were measured before administration of medication, and then serum cortisol levels were measured again 30 and 60 min after the administration of an intravenous bolus of 250 µg of ACTH. Responses were considered normal if maximum serum cortisol levels measured after bolus administration were greater than 18 µg/dL [6,7]. Once AI was confirmed by cosyntropin testing, patients were categorized as having primary or secondary AI on the basis of baseline plasma ACTH levels. AI was considered primary if plasma ACTH levels were high (>63.3 pg/mL) and considered secondary or tertiary if plasma ACTH levels were low or inappropriately normal (<63.3 pg/mL). Computed tomography (CT) or magnetic resonance imaging (MRI) scans of the brain and the pituitary glands were reviewed to investigate the etiology of secondary and tertiary AI. The corticotropin-releasing hormone (CRH) stimulation test is used to differentiate between secondary and tertiary AI. However, since secondary and tertiary adrenal insufficiencies are treated similarly, the CRH stimulation test was not performed. All hormonal test results were reviewed and confirmed by an experienced endocrinologist. The study was conducted after approval by the Institutional Review Board (IRB) at Interfaith Medical Center.

Assays

All parameters were measured using commercially available radioimmunoassay (RIAs) or immunoradiometric assays.

The sensitivity of the ACTH assay (ACTH Immunoassay, Roche Diagnostics, Indianapolis, IN, USA) was 1.0 pg/mL. The intra-assay coefficients of variation were 2.7% at 4.9 pg/mL and 0.7% at 1205 pg/mL. The normal value for plasma ACTH is 7.2–63.3 pg/mL. The sensitivity of the cortisol assay (Roche Diagnostics, Indianapolis, IN, USA) was 0.03 µg/dL. The intra-assay coefficient of variation was 1.7% at 4.69 µg/dL and 1.7% at 26.0 µg/dL. The normal value for serum cortisol is 6.2–19.4 µg/dL at 0800 h and 2.3–11.9 µg/dL at 2000 h.

Statistical analysis

Comparisons of positive cosyntropin tests and secondary variables were compared using Student's *t*-test. A *p* value of less than 0.05 was considered statistically significant. The odds ratio for positive cosyntropin tests were calculated.

Results

A total of 4053 adult patients were hospitalized in the Department of Medicine at Interfaith Medical Center between October 23, 2010, and November 23, 2011. 62 SCD patients were hospitalized for painful crisis; their general demographic characteristics are shown in **Table 1**. Morning serum cortisol levels were measured in 17 of these 62 SCD patients (**Fig. 1** shows schematic diagram of the study design). These patients were selected on the basis of low blood pressure readings and electrolyte abnormalities. Cortisol levels were lower than 18 µg/dL in all 17 patients. Cosyntropin tests were performed in 15 of the above 17 SCD patients (mean morning cortisol level of 5.4 ± 4.5 µg/dL). Test results were suggestive of AI in 12 patients (19.4%; 12 of 62 SCD patients) (**Table 2**). Mean serum cortisol levels 30 and 60 min after ACTH stimulation were low: 8.8 ± 5.3 µg/dL (30 min) and 13.4 ± 3.1 µg/dL (60 min) in the positive test group (normal: greater than 18 µg/dL). Baseline plasma ACTH levels were either low or inappropriately normal in all 12 positive test-group patients (mean: 11.4 ± 7.7 pg/mL; normal: 7.2–63.3 pg/mL). These patients were categorized as having secondary AI. Of the 12 patients with secondary AI, none had a history of head injury in the past. 8 patients had undergone MRIs or CTs of the brain and pituitary gland. The results were negative for hypothalamic or pituitary hemorrhage, infarct, or mass for all 8 patients. When SCD patients with and without AI were compared, MCV values were significantly greater in SCD patients with AI than in SCD patients without AI (85.3 ± 14.6 vs. 99.7 ± 7.9; *p* < 0.05). In contrast, many clinical parameters did not differ significantly between AI patients with SCD. These parameters included: reticulocyte count upon admission (12.3 ± 15.2 cells/µL vs. 10.0 ± 5.1 cells/µL; *p* = 0.68), LDH level upon admission (311.3 ± 145.7 IU/L vs.

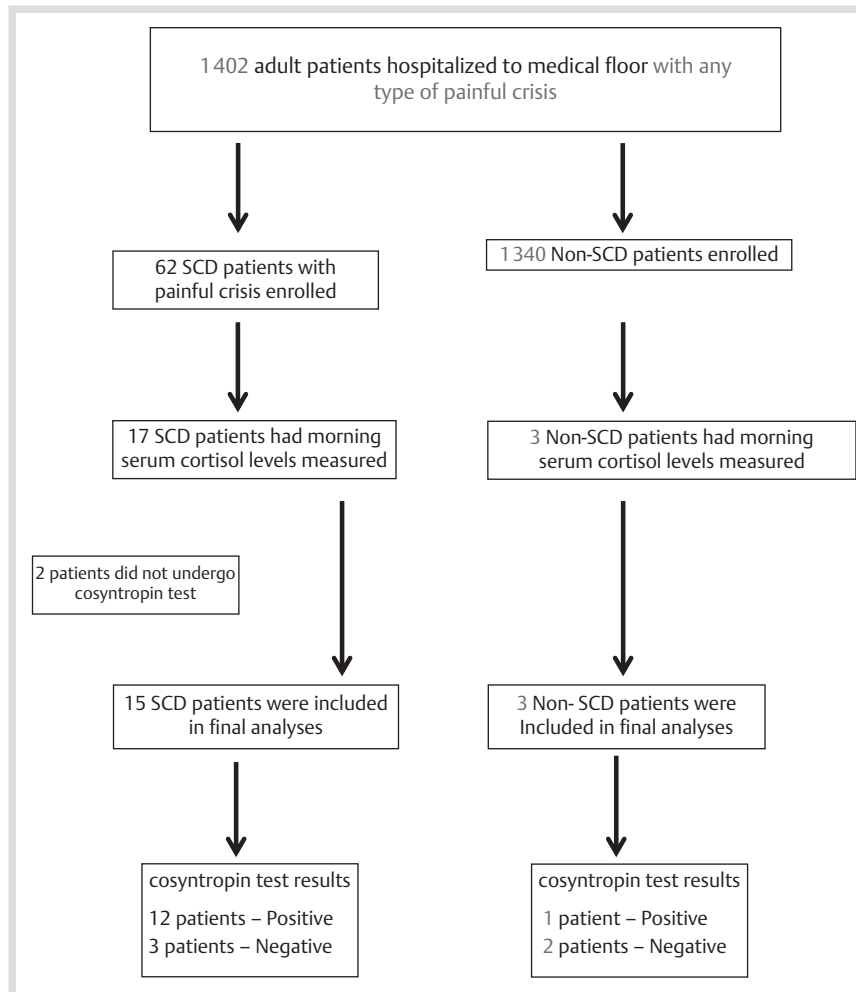


Fig. 1 Schematic Diagram of the Study Design.

Table 2 High-dose ACTH Stimulation (Cosyntropin) Test Results.

	# of Patients	Morning Cortisol	p-value	Baseline ACTH	p-value	Cortisol 30 min	Cortisol 60 min	p-value
Reference Range		6.7–22.6 µg/mL	–	7.2–63.3 µg/mL	–	> 18 µg/dL	> 18 µg/dL	–
SCD normal (A)	3	9.0±6.7	A vs. B: p<0.05	12.5±7.3	A vs. B: p=0.83	N/A	20.4±2.1	A vs. B: p<0.005
SCD AI(*) (B)	12	3.6±2.1	C vs. D: N/A	11.4±3.1	C vs. D: N/A	8.8±5.3	13.4±3.1	C vs. D: N/A
Non-SCD Normal (C)	2	11.8	B vs. D: N/A	27.0	B vs. D: N/A	N/A	30.7	B vs. D: N/A
Non-SCD AI(*) (D)	1	6.2	A vs. C: P=0.7	1.0	A vs. C: P=0.44	N/A	14.2	A vs. C: P=0.69

(*) AI=Adrenal Insufficiency

363.9±206.2IU/L; p=0.69), potassium level on test date (4.4±0.5 mEq/L vs. 4.3±0.3 mEq/L; p=0.50), transferrin saturation (55.8±20.7% vs. 38.0±9.9%; p=0.29), units of red blood cells transfused (2.7±4.6 units vs. 6.4±8.1 units; p=0.48), and the doses of opioids administered during the admission (3.9±3.4 mg/kg/day vs. 4.6±2.7 mg/kg/day; p=0.71) (◉ Table 3).

Thyroid stimulating hormone (TSH) levels were also measured in 11 of the 12 SCD patients with AI. The levels were normal in all but one patient: 1.8±1.2 µIU/mL (normal: 0.34–5.6 µIU/mL). The exception was 1 patient with low TSH level (0.33 µIU/mL). Aside from TSH levels, other pituitary hormone level including prolactin, insulin-like growth factor (IGF-1), follicular stimulating hormone (FSH), and luteinizing hormone (LH) were also

measured in a few of these patients, but the results were incomplete. In addition, the hypothalamic-pituitary-adrenal axes were not reassessed in these 12 patients after index admission.

Of the 3 non-SCD patients whose morning serum cortisol levels were measured, 3 fulfilled the inclusion criteria. Cosyntropin testing was subsequently conducted for these patients (◉ Fig. 1). Results were suggestive of AI in 1 (◉ Table 2). In other words, 1 of 1340 non-SCD patients (0.075%) fulfilled the clinical criteria for AI.

The odds ratio for AI [(12/62)/(1/1340)] was 259 in SCD and non-SCD patients. When the prevalence of AI in SCD patients was compared to that of the general population, the odds ratio [(19.4%)/(0.008%)] was 2375.

Table 3 Clinical, Laboratory, and Treatment Variables in Study Groups.

Patients group (SCD vs. Non-SCD)	Normal Range	SCD	SCD	p-value	Non-SCD	Non-SCD	p-value
		Normal	AI (*1)		Normal	AI (*1)	
patients		3/62 (4.8%)	12/62 (19.4%)		2	1	
female		3/3 (100%)	7/12(58%)		0	0	
age (yr)		39.3±12.2	33.1±10.2	p=0.39	30	23	N/A
genotype: Hb SS		2/3 (67%)	10/12 (83%)				
Hb S-β+ thalassemia		1/3 (33%)	1/12 (8.3%)				
Hb SC		0/3 (0%)	1/12 (8.3%)				
MBP on test date (mmHg)		79.0±19.1	73.7±8.5	p=0.47	85	56	N/A
systolic BP on test date (mmHg)		103.0±22.9	101.5±13.6	p=0.89	109	83	N/A
Na on test date (mEq/L)	136–144	135.3±2.5	136.7±2.3	p=0.40	125	139	N/A
K on test date (mEq/L)	3.6–5.1	4.4±0.5	4.3±0.3	p=0.50	4.5	4.5	N/A
Glu on test date (mg/dL)	74–118	90.3±38.1	105.4±33.0	p=0.52	93	100	N/A
iron (mcg/dL)	45–182	103.4±63.7	115.5±33.2	p=0.81	N/A	N/A	
ferritin (ng/mL)	11–307	1632.9±1731.1	1179.0±1558.5	p=0.74	N/A	N/A	
transferrin saturation (%)	20–50	55.8±20.7	38.0±9.9	p=0.29	N/A	N/A	
MCV (fL)	80–100	85.3±14.6	99.7±7.9	p<0.05	N/A	N/A	
reticulocyte count	0.5–1.5	12.3±15.2	10.0±5.1	p=0.68	N/A	N/A	
LDH (IU/L)	98–192	311.3±145.7	363.9±206.2	p=0.69	N/A	N/A	
morphine sulfate (mg/kg/day)		3.9±3.4	4.6±2.7	p=0.71	N/A	N/A	
units of red cells transfused/year		2.7±4.6	6.4±8.1	p=0.48	N/A	N/A	

* 1. AI: Adrenal Insufficiency

Discussion

In spite of the low prevalence of AI in the general population (0.008%), this disorder was diagnosed in 19.4% of patients with SCD in our retrospective analysis. SCD is an autosomal recessive hemoglobin disorder characterized by hemolytic anemia and intermittent occlusion of small vessels by sickling cells. This occlusion eventually leads to chronic organ damage and dysfunction [8].

There are few reports focusing on AI in SCD patients. The prevalence and pathogenesis of AI in SCD patients are therefore not clear [9,10]. Iron overload-induced endocrinopathy, vaso-occlusion/ischemia-induced endocrinopathy, and opioid-induced HPA axis dysfunction have all been considered as potential causes of AI in SCD patients [11–20].

Endocrinopathies, including AI, are among the earliest manifestations of iron overload syndrome secondary to multiple red blood cell transfusions (more than 8 units in a 12 month period) in SCD patients [11, 12]. Iron overload syndrome is a condition in which excess iron from dietary or multiple transfusions accumulates in the body and causes damage to organs. Cardiomyopathy, cirrhosis, endocrinopathy and diabetes mellitus have all been reported as examples of organ damage secondary to iron accumulation. According to previous studies, a transferrin saturation greater than 60% in men and 50% in women diagnoses iron overload syndrome in more than 90% of patients [13, 14]. In our study, 6 of our 12 SCD patients with AI had iron overload syndrome, based on their high transferrin saturation levels. However, transferrin saturation levels were normal in the remaining 6 patients. These data indicates that iron overload is not the sole contributor to AI in SCD patients.

Vaso-occlusion-induced ischemia has been implicated in the pathogenesis of endocrine dysfunction in SCD. Vaso-occlusion with or without infarction of the involved organs is not uncommon and may involve any internal organs. These organs include the brain, the pituitary gland, and the adrenal glands in SCD patients [15,16]. All cases of AI in SCD patients in this study were of central origin (secondary to pituitary or hypothalamic

dysfunction), as demonstrated by low or inappropriately normal baseline ACTH levels. Athanasou reported a case of SCD in which recent necrosis of the pituitary gland was seen upon necropsy. These data supports the above hypothesis [17]. Rosenbloom et al. noted that baseline serum cortisol levels were low in SCD patients and dropped further during vaso-occlusive crisis. These data were consistent with vaso-occlusion-induced stepwise decline in HPA axis function [10,18]. The finding that SCD patients had normal potassium levels and low or inappropriately normal baseline plasma ACTH levels suggests that the hypothalamo-pituitary complex is the main target for vaso-occlusion-induced ischemia, although MRI studies of the pituitary in SCD with AI were negative.

A possible cause of secondary AI in our SCD patients could be chronic use of opioid analgesics, as has previously been suspected by other authors [3,4,19]. Schimke reported a case of secondary AI induced by chronic use of opioids for pain management [19]. Opiates bind μ and κ -opioid receptors and exert stimulatory effects on the HPA axis. Over time, however, the HPA axis develops tolerance to the stimulatory effects of opioid agonists, and ultimately opiates inhibit the release of corticotropin-releasing factor (CRF) from the hypothalamus [20]. A subsequent decrease in ACTH production by CRF will eventually lead to low cortisol levels. The dose-ranges and duration of opioid analgesics use required to cause secondary AI are still unknown, as is the duration of the resultant HPA axis dysfunction.

Our study has some limitations. First, our study was retrospective, and the number of patients analyzed was limited. Therefore, larger studies are required in order to confirm our results. Second, cortisol levels 30 min after high-dose ACTH stimulation tests were not measured in all patients, and thus the calculated mean may not reflect the peak cortisol level. Third, CTs or MRIs of the pituitary gland and hypothalamus were not done in all patients with secondary AI. Therefore, hemorrhagic necrosis of the pituitary gland or hypothalamus cannot be ruled out in all of our patients. Fourth, it was difficult to determine the precise dose of opioids taken before the index admission. As a result, we could not characterize the pattern of opioid use that best corre-

lated with the occurrence of AI. Fifth, pituitary hormone levels other than ACTH levels were not measured in all SCD patients with AI. We therefore, could not conclude if other components of the pituitary axis might also be affected or not. Finally, we did not determine whether the HPA-axis dysfunction was transient or persistent.

Conclusion

Our retrospective analysis confirmed AI in 19.4% of SCD patients tested. These patients therefore had a 2375-fold risk of AI compared with the general population, and a 259-fold risk of AI compared with a hospitalized non-SCD population. Our study suggests that AI in SCD patients is generally secondary to hypothalamic or pituitary dysfunction. Since chronic opioid use is known to induce AI, chronic opioid use in our SCD patients may well be an instigating factor. Larger, in-depth studies are needed to determine the prevalence and pathogenesis of AI more accurately in SCD patients.

Conflict of Interest and Acknowledgements

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